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Report on NDMA/NDEA impurities in Valsartan

The following report is provided pursuant to Rule 26 of the Federal Rules of Civil Procedure. All of the opinions that I have offered in this report are given to a reasonable degree of scientific certainty, are based on the methods and procedures of science, are based on my knowledge of recognized scientific principles and methodology reasonably relied upon by members of my profession, and are based on my education, training, knowledge, experience and/or materials that I have reviewed in connection with this litigation, which are substantial. Each opinion is offered to articulate a sufficiently reliable basis for my opinions concerning this case. The facts and data set forth herein are the types of facts and data that I and other experts in the field of genetic toxicology reasonably rely upon.

Citations to specific reference material are offered in this report, where I believe it necessary to cite a specific source; otherwise, my opinions are derived from a combination of reference sources, my own experience, and my general scientific knowledge. This report is not meant to be an exhaustive recitation of all of my opinions in the above-referenced cases. I reserve the right to amend and supplement the opinions expressed in this report and in response to any opinions offered by Plaintiffs' experts at their depositions or at trial.

I.   Purpose and Scope of Report

I have been asked on behalf of Defendants in this case to provide an independent evaluation of the toxicology of *N*-nitrosodimethylamine ("NDMA") and *N*-nitrosodiethylamine ("NDEA"). I have been asked in particular to focus on the risk assessment for the trace levels of NDMA and NDEA discovered in 2018 in valsartan tablets used primarily in the treatment of hypertension. This evaluation includes a calculation of the Permissible Daily Exposure ("PDE") for these impurities utilizing the Benchmark Dose Method ("BMD"). I have also been asked to review and respond to the opinions and assertions contained in the reports offered by Dr. Lagana, Dr. Panigrahy, Dr. Etminan, and Dr. Hecht. I have formed my opinions to a reasonable degree of scientific certainty on these

subjects as set forth in this report, and would testify to them if called as a witness at trial or deposition.[1]

II.   Background/Qualifications

I am currently an Associate Professor at the Swansea University in Wales, U.K, and have been on the faculty since 2006. I have a primary appointment in the Department of Genetic Toxicology. I currently serve as a member of the Steering Committee of the Health and Environmental Sciences Institute (HESI), Genetic Toxicology Technical Committee (GTTC). I am presently a co-leader of the International Workgroup on Genetic Toxicology (IWGT) quantitative group, methods and metrics subgroup.

I received a Bachelor of Science degree in Genetics from Swansea University in 2002 and completed my Ph.D. in 'Mechanistic Investigations of the Quantitative and Qualitative Effects of Genotoxicants in 2006 at Swansea University, along with achieving a Teaching in Higher Education postgraduate certificate in 2013. I won the prestigious UK Environmental Mutagen Society (UKEMS) young scientist award in 2012 and the European EMS (EEM[G]S) young scientist award in 2014.

In my current position, I teach or have taught graduate students (Ph.D. post doctoral fellows as well as Ph.D. and masters candidates) and undergraduate students in the areas of genetic toxicology, including mutagenic impurities, cancer biology and DNA repair. I provide information on determining dose-response levels of various impurities, including nitrosamines, and teach how mutagenic toxicants are metabolized, and the mechanics of the mutagen in damaging DNA, any DNA repair mechanisms and any resulting carcinogenetic effect. I have studied and published extensively on how both animal and human cells respond

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[1] This report contains my opinions regarding general causation only, as requested by counsel. This report is not intended to be an exhaustive recitation of all of my opinions in this litigation, and I expressly reserve the right to amend or supplement this report to offer additional opinions, including opinions on liability, specific causation, damages, or other defenses, at the appropriate stage of litigation.

to mutagenic impurities, including their molecular and cellular mechanisms of action. I also teach through the American College of Toxicology a course on Practical Application of Toxicology in Drug Development. I have delivered GeneTox courses run in Edinburgh, Cambridge and online. I also have delivered workshops on quantitative approaches in genetic toxicology in risk assessment. Since the events which resulted in the NDMA/NDEA impurities in valsartan, I have also lectured extensively on this topic.

In addition to my teaching responsibilities, I direct an active laboratory at Swansea University Medical School and am actively engaged in numerous research studies programs in various areas of toxicology, and in particular studying the dose-response and threshold mechanisms of NDMA and NDEA. I have published 65 original research articles in peer reviewed journals in my field, along with dozens of meeting abstracts, related to toxicology, mutagenic carcinogens, and DNA repair. Some of these publications have focused on my research on NDMA and NDEA, and they include a chapter entitled "Genotoxic Impurities" in the Second Edition of "Mutagenic Impurities." In recognition of my expertise in these areas, I have served on and/or chaired numerous national and international research review committees that make recommendations on priorities for research funding. I have also served as a peer reviewer for multiple journals in my field. Additional experience, presentations, and publications on this subject are reflected on my *curriculum vitae* attached as Exhibit A.

III.   **Disclosures**

My *curriculum vitae*, which details my education and experience, and includes a list of publications authored by me, is attached to this report as Exhibit A. A list of the materials which I have considered is attached to this report as Exhibit B. In addition to documents identified in Exhibit B, my opinions are based on my knowledge, research and experience with the toxicology of mutagenic carcinogens in particular. I expressly reserve the right to supplement the list in Exhibit B if needed during the course of this litigation. Additionally,

my customary fee for professional services, including my study and testimony in this matter, is

£150 per hour. I have not given testimony in deposition or trial in the past four (4) years.

IV.   Methodology

In my evaluation and analysis of this matter I utilized the same methodology and

scientific analysis that I use in my professional life as an active toxicology researcher and

scientific journal reviewer, and applied my education, training and experience in toxicology

to my analysis. I did and continue to do independent research of the relevant issues in this

litigation pertaining to mutagenic carcinogens, and NDMA in particular, as well as research

on the DNA repair in humans and the non-linear extrapolation method to determine the level

of NDMA exposure that is of no increased risk to humans. My independent research in this

case included reviewing related articles on PubMed among other sources, as well as

consulting the toxicology textbooks I teach from.

V.   Relevant Background on NDMA/NDEA in Valsartan

This litigation arises from a situation in which the unexpected impurities NDMA and

later NDEA were found in certain lots of valsartan made by various manufacturers.   On June

22, 2018, ZHP notified the European authorities that it had discovered the presence of a

previously undetected impurity, which was later identified as NDMA. According to tests of a

random selection of API batches performed by ZHP, the levels of NDMA ranged from 3.4

ppm to 120 ppm, with an average of 66.5 ppm.

The discovery of NDMA in ZHP's valsartan led to a rapid EU product recall of

affected batches.[2] European Medicines Agency's ("EMA") findings of NDMA in valsartan

API from ZHP had world-wide ramifications. Based on information received from EMA, the

U.S. Food and Drug Administration ("FDA") also reported NDMA in ZHP's API and

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[2] EMA, EMA reviewing medicines containing valsartan from Zhejiang Huahai following detection of an impurity: some valsartan medicines being recalled across the EU (2018a).

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finished dose products sold in the United States.[3] On August 9, 2018, FDA also confirmed an

N-nitrosamine recall of valsartan medicinal products from Hetero Labs Ltd in India.[4] By the

end of August 2018, FDA indicated that sixteen suppliers of valsartan API to the US market

had been implicated. The manufacturers of the affected valsartan issued a voluntary recall of

all of its valsartan products within expiry that were manufactured with this potential impurity.

Later, in November 2018, some batches of valsartan API manufactured by Mylan

Laboratories Ltd. ("Mylan") were found to contain trace levels of NDEA. As a result, Mylan

and Teva issued voluntary recalls of their valsartan products within expiry that were

manufactured with Mylan's API.

In 2018, Aurobindo Pharma LTD ("Aurobindo") identified trace amounts of NDEA in

some of its valsartan API caused by NDEA-containing recovered Tri N Butyl Tin Chloride

obtained from Lantech Pharmaceutical Limited and an absence of change over cleaning

procedures by Logistical Services Providers which allowed for the introduction of

Triethylamine (TEA), which reacted with sodium nitrite and formed NDEA.[5]

The FDA published the results of testing of NDMA-containing valsartan products, as

follows:

Table 1: NDMA in Valsartan Reported by FDA[6]

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[3] FDA, News Release: FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity (July 13, 2018).

[4] FDA, News Release: FDA Updates recalled valsartan-containing product information (Aug. 9, 2018).

[5] *See* Aurobindo's Initial Response to FDA's Warning Letter (APL-MDL 2875-0004189), pp 1-6.

[6] FDA, Laboratory Analysis of Valsartan Products, FDA.gov, https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products (last updated May 2, 2019) (midpoint calculations added). The level of nitrosamines present in recalled finished dose products is a more accurate measure of what, if any, nitrosamine exposure a consumer might have experienced, than the level present in the valsartan API. Notably, as evidenced by testing of Aurobindo valsartan API batches compared to corresponding final products, nitrosamine levels are reduced during the preparation of the final drug. Thus, it would be inaccurate to conclude, as Dr. Hecht does, that "the NDMA and NDEA levels would be expected to be the same or nearly so in the finished dose formulation incorporating the contaminated valsartan API." *See, e.g.*, Aurobindo's finished product testing (APL-MDL 2875-0139456; AURO-MDL 2875-0113984-89) and Aurobindo's API testing at Annexure-1 to Aurobindo's Response to FDA's General Advice Letter (APL-MDL 2875-0011138).

Company	Product (tablets)	Lots Tested	NDMA level micrograms – (mcg)/tablet (midpoint ("MP"))	NDEA level micrograms – (mcg)/tablet (midpoint ("MP"))
Aurobindo Pharma Ltd	Amlodipine 10mg/Valsartan 320 mg	VKSA18005-A, VKSA18007-A, VKSA18001-A	Below LOD	0.02-0.09 MP = 0.055
Aurobindo Pharma Ltd	Valsartan 320mg	VUSD17008-A, VUSD17001-A, VUSD17009-A	Below LOD	0-0.05 MP = 0.025
Aurobindo Pharma Ltd	Valsartan 320mg/HCT 25mg	HTSB18001-A, HTSB18028-A, HTSB18029-A	Below LOD	0.02-0.19 MP = 0.105
Hetero Labs Ltd	Valsartan 320mg	VLS18049, VLS18051, VLS18050	0.33-0.44 MP = 0.385	Below LOD
Mylan Pharmaceutical Inc.	Amlodipine 10mg/Valsartan 320 mg	3079709, 3077618, 3079708	Below LOD	0.04-0.11 MP = 0.075
Mylan Pharmaceutical Inc.	Amlodipine 10mg/Valsartan 320 mg/HCT 25mg	2008702	Below LOD	0.05
Mylan Pharmaceutical Inc.	Valsartan 320mg	3080009, 3080010, 3079205	Below LOD	0.07-0.16 MP = 0.115
Mylan Pharmaceutical Inc.	Valsartan 320mg/HCT 25mg	3084886, 3093804, 3084862	Below LOD	0.20-0.38 MP = 0.29
Prinston Pharmaceutical	Valsartan 320mg	344B18027, 344B18028, 344B18029	15.18-16.30 MP = 15.74	Below LOD
Prinston Pharmaceutical	Valsartan 320mg/HCTZ 25mg	611B18025, 611B18026, 611B18027	13.18-20.19 MP = 16.69	Below LOD
Teva Pharmaceutical	Amlodipine 10mg/Valsartan 320 mg	26X053, 26X054, 26X055, 26X051, 26X044, 26X048	Below LOD	0-0.03 MP = 0.015
Teva Pharmaceutical	Amlodipine 10mg/Valsartan 320 mg/HCT 25mg	22X045, 22X046, 22X047, 22X038, 22X041	Below LOD	0-0.03 MP = 0.015
Teva Pharmaceuticals	Valsartan 320mg	1240425A, 1247282M	7.92-16.55 MP = 12.24	Below LOD

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Company	Product (tablets)	Lots Tested	NDMA level micrograms – (mcg)/tablet (midpoint ("MP"))	NDEA level micrograms – (mcg)/tablet (midpoint ("MP"))
Teva Pharmaceuticals	Valsartan 320mg/HCTZ 25mg	1217576M, 1217577M, 1217578M	6.94-10.35 MP = 8.65	0-0.77 MP = 0.385
Torrent Pharmaceuticals	Amlodipine 10mg/Valsartan 320 mg/HCTZ 25mg	BBX2E001, BBX2E002, BBX2E003	10.24-11.53 MP = 10.89	Below LOD
Torrent Pharmaceuticals	Valsartan 320mg	BV48D001, BV48D002	0.56-0.62 MP = 0.59	1.12-1.22 MP = 1.17
Torrent Pharmaceuticals	Valsartan 160mg	BV47D001	0.45	1.31

In the above chart, I have added the midpoint ("MP") of each range, recognizing that the range determined by FDA reflects a number of testing outcomes and the midpoint of those outcomes is the assessment we can make of the level of NDMA/NDEA to which the average patient could reasonably be expected to be exposed.[7]

Additionally, my risk assessment and opinions in this case address the claimed risks associated with the various levels found in the finished dose valsartan tablets, which I have averaged since no patient would have taken just a single batch over the 70 year lifetime calculation. I have done the same for each generic manufacturer who was affected by the impurities and took the average of those levels as well and reached an overall average of the levels of NDMA and NDEA found in the various manufacturers' valsartan products.

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[7] I understand the manufacturers listed in Table 1 also conducted their own testing of their valsartan API and/or valsartan finished dose product. For purposes of this report, I am focusing on the levels of NDMA/NDEA detected in the finished dose products, as opposed to API, because ultimately finished dose product is what reaches patients. And to frame my opinions, I am relying upon the testing data reflected on FDA's website, which appears to be representative of the levels reflected in the Defendants' internal testing. However, to the extent those values may be higher or lower than the figures set forth in the referenced table, my opinion remains the same that trace levels of NDMA and/or NDEA detected in the manufacturers' valsartan-containing medication do not increase the risk of cancer in patients.

VI.   Introduction to Mutagenic Impurities

A. What are Mutagenic Impurities?

Mutagens are chemicals, substances, or other agents that cause a mutation, or change, in the DNA sequence within a cell. Mutagenicity refers to an agent's capacity to cause such genetic alterations. Impurities may be natural or man-made; in the pharmaceutical context, for example, impurities include organic, inorganic, or residual solvents that are created during manufacturing or storage of a pharmaceutical drug product. Where the impurity is natural or created endogenously, they are referred to as "toxins," and when the compound is man-made they are referred to as "toxicants." "Mutagenic impurities" thus refers to natural or man-made compounds or agents that have potential to cause DNA mutations. Both NDMA and NDEA are mutagenic impurities.

A related term, genotoxicity, refers to an agent's capacity to cause damage to DNA, which may include mutations or other non-mutagenic changes. Thus, an agent that is mutagenic is necessarily genotoxic, but an agent that is genotoxic is not necessarily mutagenic. Additionally, certain mutations are known to result in cancer, rendering the responsible mutagens not only mutagenic but also carcinogenetic.

There are three false assumptions concerning mutagenic impurities: 1) that mutagens are rare; 2) that genotoxicity dose-response functions do not contain a low-dose region mechanistically characterized by zero-order kinetics; and 3) that genotoxicity is not a bona fide toxicological endpoint.[8] These false assumptions are all reflected in the reports and the bases for the opinions I have reviewed from Plaintiffs' expert witnesses and are in part the reasons why I disagree with the opinions contained in those reports.

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[8] White, P.A., et al., Quantitative Interpretation of Genetic Toxicity Dose-Response Data for Risk Assessment and Regulatory Decision-Making: Current Status and Emerging Priorities, Environmental and Molecular Mutagenesis 61:66-83 (2020).

Mutagens are not rare. In fact, they are present in the environment, in everyday food and beverages and in some drinking water. Risk assessments on mutagenic impurities like NDMA/NDEA therefore should not be done in an overly conservative way, as humans are exposed to low levels of very potent mutagenic carcinogens every day and at those levels (many of which are higher than the levels of NDMA/NDEA impurities detected in valsartan) the population is not at risk.

Notably, damage to the DNA sequence, including damage done by mutagenic impurities, may be remedied by the body's own DNA repair mechanism. Specifically, there are a series of evolutionarily conserved DNA repair enzymes, that can recognise and repair specific DNA damage. A lot of DNA damage occurs endogenously, along with through exposure in food and the environment, therefore living organisms have evolved DNA repair pathways for all common types of DNA damage. Smaller chemical modifications to DNA, including addition of alkyl groups (e.g. CH_3, C_2H_5) to certain bases, can be directly removed by suicide enzymes such as alkyl guanine alkyltransferase (AGT/MGMT), or if they appear in less critical positions of DNA, can be recognised by certain DNA glycosylase enzymes before base excision repair ("BER") fully repairs the DNA damage.

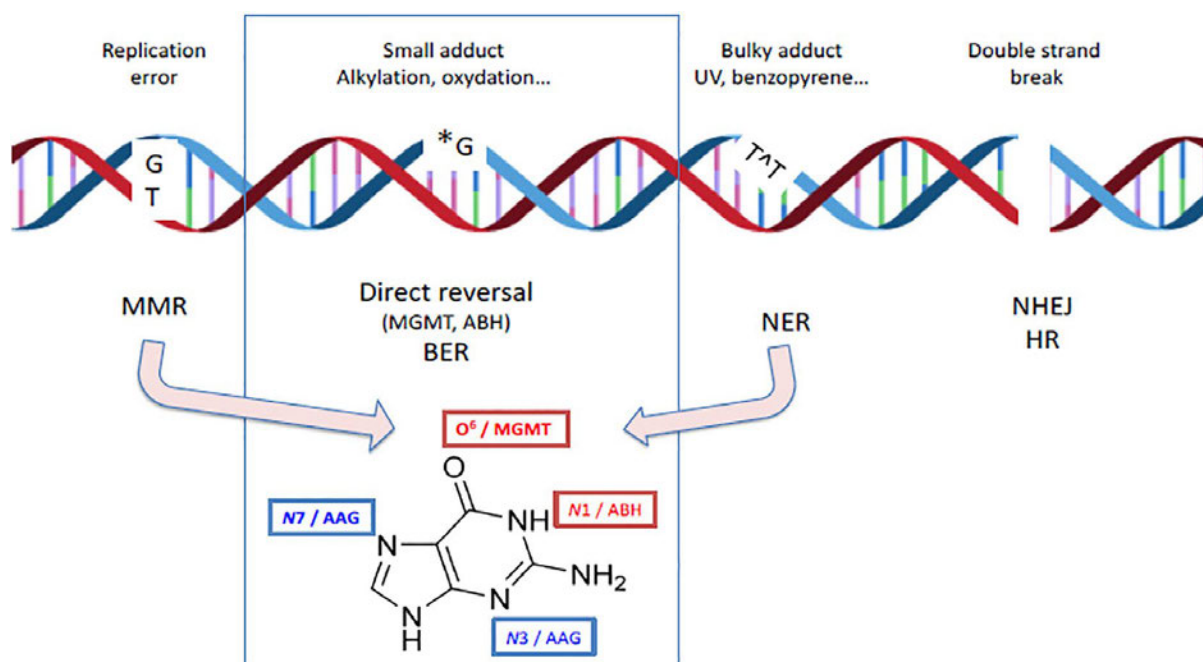Several other DNA damage types, and corresponding DNA repair pathways, are illustrated in **Figure 1** below.

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Figure 1[9]: Schematic of DNA damage types and corresponding repair pathways. MMR, mismatch repair; BER, base excision repair; MGMT, methyl guanine methyltransferase; NER, nucleotide excision repair; NHEJ, non-homologous end-joining; HR, homologous recombination; AAG, alkyladenine DNA glycosylase; ABH, AlkB homologous proteins.

B. Nitrosamines such as NDMA and NDEA are mutagenic impurities which are common in the environment and diet.

There are over 300 nitrosamines that differ in mutagenic and carcinogenic potency. *N*-Alkyl-nitrosamines, such as *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA), are well-studied, common environmental mutagens. NDMA/NDEA and other mutagenic compounds are common in every-day food and beverages, as demonstrated in **Figure 2** below.

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[9] Pottenger LH, Boysen G, Brown K, Cadet J, Fuchs RP, Johnson GE, Swenberg JA, Understanding the importance of low-molecular weight (ethylene oxide- and propylene oxide-induced) DNA adducts and mutations in risk assessment: Insights from 15 years of research and collaborative discussions, Environ. Mol. Mutagen 60(2):100-121 (2019).

BACKYARD BARBECUE MENU

- Smoked Brisket: 4-4,000 ng/kg NDMA; 6 – 9000ng/kg NDEA
- Bacon: .76 – 3.92 μg/kg NDMA, 0.17 - .77 μg/kg NDEA
- Fried Fish: 0.169 μg/100g NDMA, 0.088 μg/100g NDEA
- Sausage: 10.941 μg/100g NDMA, 0.040 μg/100g NDEA
- Hot Dogs: 0.221 μg/100g NDMA
- Sauerkraut: 0.660 μg/100g NDMA, 0.079 μg/100g NDEA
- Ham: 0.18 – 3.45 μg/kg NDMA, 0.2 - .77 μg/kg NDEA
- Oysters: 1.139 μg/100g NDMA, 0.109 μg/100g NDEA
- French Fries: 0.024 μg/100g NDMA
- Rolls/Buns: 0.050 μg/100g NDMA, 0.023 μg/100g NDEA
- Butter/Margarine: 0.026 μg/100g NDMA
- Refried Beans: 0.033 μg/100g NDMA
- Cottage Cheese: 0.076 μg/100g NDMA, 0.057 μg/100g NDEA
- Beer: 0.202 μg/100g NDMA
- White Wine: 0.025 μg/100g NDMA

Figure 2: NDMA and NDEA levels in common food products.[10]

Nitrosamines have been studied extensively in animals. NDMA and NDEA in particular are known genotoxic carcinogens in the animals studied. The most comprehensive carcinogenicity dose-response data available from rat studies indicates the liver is the most sensitive target for tumourigenicity.[11] However, there are no studies on NDMA/NDEA administration in humans, and there is no scientific evidence that these substances are carcinogenic in humans.

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[10] *See* Stuff JE, Goh ET, Barrera SL, Bondy ML, Forman MR. 2009. Construction of an N-nitroso database for assessing dietary intake. Journal of food composition and analysis. 22:S42-7; Park JE, Seo JE, Lee JY, Kwon H. 2015. Distribution of Seven N-Nitrosamines in Food. Toxicol Res 31(3):279-88. doi: 10.5487/TR.2015.31.3.279. Erratum in: Toxicol Res. 2018 Oct;34(4):371

[11] Peto, R et al., Effects on 4080 Rats of Chronic Ingestion of Nitrosodiethylamine or N-Nitrosodimethylamine: A detailed dose response study, Cancer Research 51:6415-6451 (1991) ("Peto et al. 1991a"); Peto R, Gray R, Brantom P, Grasso P, Dose and time relationships for tumor induction in the liver and esophagus of 4080 inbred rats by chronic ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine, Cancer Res. 51(23 Pt 2):6452-69. PMID: 1933907 (1991) ("Peto et al. 1991b").

C. The most precise method of conducting a hazard or risk assessment for mutagenic-carcinogenic compounds is the Benchmark Dose Method (BMD).

Hazard and risk assessment of genotoxic carcinogens, which are used to protect the human population from increased risk of cancer and genetic disease, has evolved over time with improved technology and understanding of DNA repair mechanisms. FDA and other regulators recognize this and authorize alternative risk assessments where there is sufficient data—i.e. a cancer bioassay—to depart from the older TD50 method that back-extrapolates from animal studies, and calculate a permitted daily exposure (PDE) that is typically much higher than the TD50 value that fails to consider the human factors.

Data supporting a PDE comes from cancer bioassays. The Organisation for Economic Co-operation and Development ("OECD") provides a standardized and harmonized protocol "to observe animals for a major portion of their life span for the development of neoplastic lesions during or after exposure to various doses of a test substance by an appropriate route of administration."[12] The test guideline recommends certain key study design aspects, including use of rats or mice, with both sexes used and at least 50 animals of each sex and at least three dose levels plus concurrent control, primarily using oral administration unless toxicokinetic profile of the substance requires a different route, and continues with clear guidelines for how robust data across each tissue can be compiled.[13] Deviation from the protocol causes major issues for use in risk assessment, and studies abiding to the guideline set the precedence for suitable test data. The 2-year cancer bioassay in rodents is the gold standard test used to generate dose-response data, from which metrics are calculated and then used to derive human exposure limits (e.g., the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH")).[14] Peto et al. did

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[12] OECD Guidelines – Overview, https://www.oecd.org/env/test-no-451-carcinogenicity-studies-9789264071186-en.htm.
[13] *Id.*
[14] OECD, Test No. 451: Carcinogenicity Studies (2018), available at https://www.oecd.org/env/test-no-451-carcinogenicity-studies-9789264071186-en.htm.

a cancer bioassay study of NDMA in 1991 on an exceptionally large sample size, and the

results provide sufficient data concerning threshold limits—i.e., tolerance of NDMA—to

allow for calculation of a PDE in humans.[15]

As previously mentioned, NDMA and NDEA are extensively studied compounds, as

they are found in food products and water supplies and have been studied in animals for

decades.[16] Therefore, when NDMA was detected in batches of valsartan, risk assessments

were carried out by regulators like FDA using these excellent, published data derived from

animal studies. The risk assessment FDA utilized is the TD50 back-extrapolation by which

FDA calculated an Acceptable Intake ("AI") level.[17] However, the TD50 has severe

limitations in attempting to predict carcinogenicity in humans. The outcome reflects an

overly conservative limit that ignores the metabolism and DNA repair that NDMA and

NDEA are subject to. For example, the TD50 does not have adjustment factors; it merely

back extrapolates from the animal data. As such, the 1 in 8,000[18] or 1 in 100,000[19] cancer

risk that FDA stated in its press releases relates to the test species population and not the

human population. Additionally, the animal studies cited in the reports of Drs. Lagana,

Panigrahy, Hecht, and Etminan represent nothing more than evidence of carcinogenicity in

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[15] Peto et al. 1991a; Peto et al. 1991b.

[16] Despite the extensive studies, NDMA and NDEA have remained classified only as "probable human carcinogens." As defined by IARC, "probably carcinogenic to humans" is defined as follows: "[T]here is strong evidence that it can cause cancer in humans, but at present it is not conclusive." Scientific Committees Toolbox, Standard IARC Classification, https://ec.europa.eu/health/scientific_committees/opinions_layman/en/electromagnetic-fields/glossary/ghi/iarc-classification.htm (last visited Aug. 1, 2021).

[17] To clarify what the AI means, it is not a level below which there is no effect and above which it causes cancer. The AI reflects an extremely conservative level that reflects an acknowledgment that the human body can handle a certain level of NDMA/NDEA without an increased risk of cancer.

[18] FDA, Statement on the Agency's Ongoing Efforts to Resolve Safety Issue with ARB Medications, https://www.fda.gov/news-events/press-announcements/statement-agencys-ongoing-efforts-resolve-safety-issue-arb-medications (Aug. 28, 2019).

[19] FDA, Update – Analysis of N-nitrosodimethylamine (NDMA) Levels in Recalled Valsartan in the U.S., https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan (July 27, 2018).

those animals at the doses received.[20] It does not matter how many species were studied at

doses sufficient to induce carcinogenicity; one cannot extrapolate to conclude humans will

also develop these cancers. Those studies are not evidence that NDMA is a human

carcinogen when ingested at trace levels in the finished dose tablets of valsartan.

A more precise risk assessment than the TD50 can be performed to evaluate the trace

levels of NDMA/NDEA in valsartan using the Benchmark Dose (BMD) approach. If a non-

linear dose response can be supported, and a threshold mechanism displayed through

biological mechanisms such as DNA repair or metabolism, the BMD method can be used to

calculate the permitted daily exposure (PDE) value. This approach is recognized by FDA, as

well as by the EMA in the ICHM7 which FDA has adopted in its current guidance on

Nitrosamines.[21] The BMD approach includes biological characterization and dose response

analysis, and provides a more precise estimate of the human exposure limit, below which the

human population can be considered to have no increased risk of cancer.

As discussed below, through these calculations that I have performed and published in

peer-reviewed journals, the patients exposed to the valsartan drug products with levels of

NDMA below 6.2μg/day (Upper Limit 10.7) (50kg person) or 12.4μg/day (Upper Limit

21.4μg) (100kg person) do not have an increased risk of cancer.[22] These numbers—

6.2μg/day (Upper Limit 10.7μg) and 12.4μg/day (Upper Limit 21.4μg/day)—represent the

Permitted Daily Exposure (PDE) of NDMA in a 50kg patient and 100kg patient, respectively.

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[20] *See, e.g.*, Kuwahara, A., Otsuka, H. & Nagamatsu, A, Induction of hemangiomatous lesions with dimethylnitrosoamine: influence of route of administration and strain of mice, Gan 63, 499-502 (1972); Terracini, B, et al., Hepatic pathology in rats on low dietary levels of dimethylnitrosamine, British Journal of Cancer 21:559-565 (1967); Tomatis, L. & Cefis, F, The effects of multiple and single administration of dimethylnitrosamine to hamsters, Tumori 53, 447-451 (1967); Campbell, J. S., Wiberg, G. S., Grice, H. C. & Lou, P, Stromal nephromas and renal cell tumors in suckling and weaned rats, Cancer Res. 34, 2399-2404 (1974); Arai, M, et al., Long-term experiment of maximal non-carcinogenic dose of dimethylnitrosamine for carcinogenesis in rats, Japanese Journal of Cancer Research 70:549-558 (1979).

[21] FDA, Guidance for industry: Control of nitrosamine impurities in human drugs (Feb. 2021).

[22] *See* Johnson, GE et al., Permitted daily exposure limits for noteworthy N-nitrosamines, Environmental and Molecular Mutagenesis 62:293-305 (2021).

Additionally, patients exposed to NDEA below 2.2µg/day (Upper Limit 4.6) (50kg person) or

4.4µg/day (Upper Limit 9.2µg) (100kg person) do not have an increased risk of cancer.[23]

These numbers—2.2µg/day (Upper Limit 4.6µg) and 4.4µg/day (Upper Limit 9.2µg/day)—

represent the Permitted Daily Exposure (PDE) of NDEA in a 50kg patient and 100kg patient,

respectively. For any amount of NDMA or NDEA exposure below the PDE, there is no

increased risk of cancer caused by the NDMA or NDEA exposure. For daily human exposure

to levels of NDMA higher than these PDE levels, I have seen no evidence of cancer being

caused in humans within an order of magnitude higher than the PDE. With respect to the

levels of NDMA and NDEA found in batches of valsartan specifically (**Table 1**), many of the

exposure levels were below the PDE and thus did not create any increased risk of cancer. For

certain batches of valsartan that had NDMA levels slightly above the PDE, there is no

evidence that NDMA at those residual levels would cause cancer in humans.[24]

VII.   Toxicology of Mutagenetic-Carcinogenic Compounds

An old adage in toxicology is: "The dose makes the poison." Just about anything can

become toxic if ingestion or exposure reaches a certain level. Toxicological analysis of

mutagenic compounds like NDMA/NDEA utilizes dose-response relationships as a basic

means of identifying the toxicity (responses) and potency (toxic doses) that determine a

chemical's relative hazards. Animal groups are given increasing doses of a studied compound

until either a toxic effect is observed in 50% of the animals (TD50) or the dose is lethal

(LD50). Such animal studies are frequently used to understand the toxicology of substances

which cannot be tested on humans, but animal data has limited utility in attempting to

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[23] *See id.*; *see also* Tables 1 and 4 and Figure 11 herein.
[24] The greatest amount of NDMA found in any single batch of valsartan was 20.19 µg/tablet, which is 9.49 µg above the PDE. I have seen no evidence that NDMA exposure at 9.49 µg above the PDE would cause or increase the risk of cancer in humans.

extrapolate risk to humans because the toxicity response is not the same between species and

therefore the conclusions derived from animal studies cannot be directly applied to humans.

A. **The mechanism of toxicity by which mutagenic impurities act is by damaging the DNA replication, i.e. causing mutation.**

DNA contains the codes for all of our cells, tissues and organs. DNA consists of

extensive sequences of only four nucleotides: adenine (A), thymine (T), guanine (G) and

cytosine (C) (seen in **Figure 3** below). Adenine pairs with thymine, and cytosine pairs with

guanine. A DNA molecule consists of two strands wound around each other, with each

strand being held together by bonds between the bases. The sequence of the bases in a portion

of a DNA molecule is called a gene, which carries the instructions needed to assemble a

protein. During cell division the DNA strand unwinds, separates and is then reattached in a

new strand, and this process ultimately leads to cell growth, tissues and organs. DNA is

replicated in specific locations, and in a very predictable, controlled manner. It is when the

DNA/cell replication proliferates out of control without the benefit of DNA repair

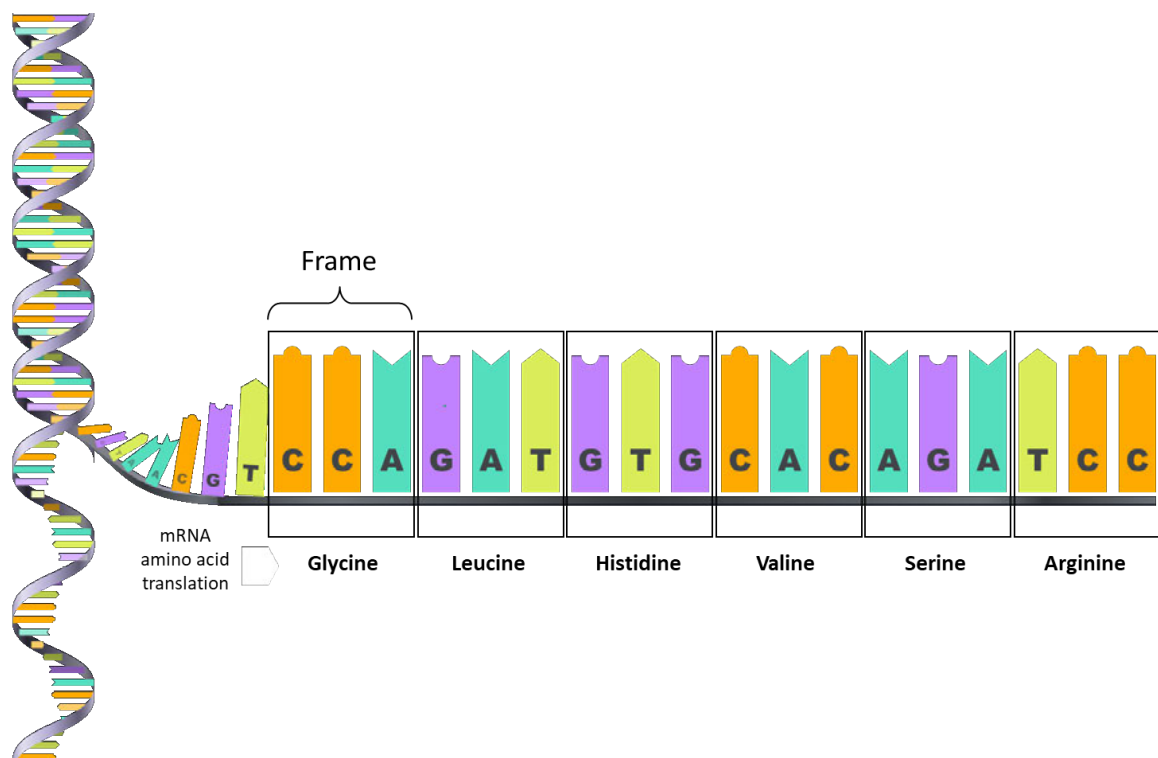mechanism(s) that a neoplasm or cancer can develop.

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Figure 3: DNA double helix, showing base pairing and the triplet codon of mRNA, and its coding for amino acids.

Mutations are permanent, and occasionally inherited, changes to the genetic material, or DNA, of a cell. During cell division, copying errors can result from damaged bases (e.g., Alkyl-Guanine) and have the potential to cause mutations which can alter the gene product (i.e., protein). These errors usually occur during replication by exposure to radiation, chemicals, or viruses, or can occur deliberately under cellular control during processes such as meiosis or hypermutation.[25] Mutations are subdivided into germline mutations (passed onto progeny) and somatic mutations which are capable of leading to neoplasia (cancer) or cell death.[26] Interestingly, mutations are considered the driving force of evolution. Whereas deleterious mutations can be removed from the gene pool by natural selection, more beneficial ones tend to accumulate in the population. Also present are neutral mutations which accumulate over time but aren't deleterious.[27]

For DNA-interacting mutagens such as alkylating agents, their mutagenicity is related to the ability to form crosslinks and/or transfer an alkyl group to form monoadducts in DNA.[28] Genotoxicity may result from critical DNA alkylation lesions, and can lead to genomic instability (as shown in **Figure 4** below). Furthermore, the genotoxicant is said to be mutagenic if this genomic instability results in mutation. Genomic instability is characterised by the increased rate of acquisition of DNA alterations in the mammalian genome. This all embracing term encompasses a multitude of diverse biological endpoints including: (i) chromosomal aberrations (chromosome- and chromatid type), (ii) karyotypic abnormalities

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[25] Friedberg, E.C., Walker, G.C., Siede. W., Wood, R.D., Schultz, R.A., Ellenberger. T, DNA Repair and Mutagenesis (2006).
[26] Klug, W. S., M. R. Cummings, Essentials of Genetics (5th ed. 2005).
[27] Griffiths AJF, Gelbart WM, Lewontin RC, Wessler SR, Suzuki DT, Miller JH, An Introduction to Genetic Analysis (8th ed. 2004).
[28] Sanderson BJ, Shield AJ, Mutagenic damage to mammalian cells by therapeutic alkylating agents, Mutat. Res. 17;355(1-2):41-57 (1996).

(fragile sites and aneuploidy), (iii) sister chromatid exchanges (SCE), (iv) micronuclei formation, (v) gene mutation and amplification, (vi) rate of cell division is altered by certain mutations resulting in variations in colony size, (vii) delayed reproductive cell death and (viii) cellular transformation.[29]
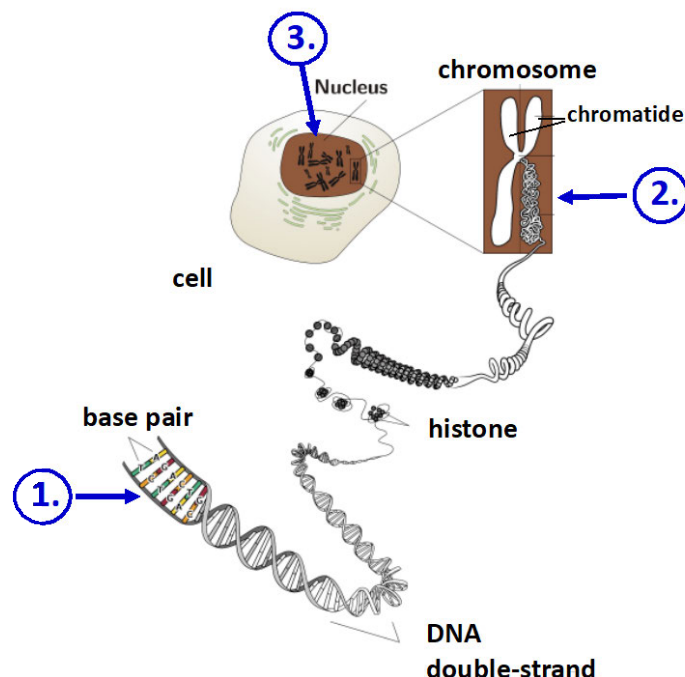

Figure 4: DNA damage induced by 3 different types of genotoxic compound: 1.) gene mutation (changes in the sequence of bases), "mutagenicity"; 2.) chromosome mutation (structural alteration), "clastogenicity"; and 3.) genome mutation (numerical chromosome alteration), "aneuploidy."

A mutagenic carcinogen acts by damaging DNA replication, which leads to gene mutation, which in turn gives rise to altered proteins.[30] These mutation events may occur over a long period of time and transpire in the context of chronic exposure to carcinogens, which can lead to the induction of human cancer at high doses and chronic exposure.[31]

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[29] Morgan WF, Day JP, Kaplan MI, McGhee EM, Limoli CL, Genomic instability induced by ionizing radiation, Radiat. Res. 146(3):247-258 (1996).
[30] Basu, A., DNA Damage, Mutagenesis and Cancer, Int. J. Mol. Sci. (2018), available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5979367/.
[31] *Id.* (emphasis added).

NDMA and NDEA act by modifying levels of certain DNA, which, in turn, cause changes in the points of departure ("PoD") for DNA sequencing.[32] The mutagenic DNA modification is known as a O^6-alkyl-G adduct—that is what NDMA and NDEA causes. AGT/MGMT is the enzyme that recognizes and removes the O^6-alkyl-G DNA adduct. If the alkyl group is not removed, upon replication, O^6-alkyl-G is mis-recognised as adenine and is paired with thymine (GC$\rightarrow$AT).

B. NDMA and NDEA require metabolism and unchecked DNA mutation before they have potential to become carcinogenic.

Merely being exposed to a mutagenic impurity like NDMA or NDEA is not sufficient to cause cancer. For a mutagenetic-carcinogenetic compound to actually create the mutation to a DNA molecule necessary to cause the cell proliferation, i.e. a neoplasm, a two-step process is required: metabolism and unchecked mutation. Nitrosamines are known to be metabolised to DNA reactive mutagens that result in methylation (alkylation) at the O^6 position of guanine,[33] the O4 position of thymidine,[34] and other less mutagenic lesions[35]. It is well established that NDMA becomes toxic only upon metabolism by the specific

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[32] Thomas, A.D., Jenkins, G.J., Kaina, B., Bodger, O.G., Tomaszowski, K.H., Lewis, P.D. et al., Influence of DNA repair on nonlinear dose-responses for mutation, Toxicological Sciences 132(1), 87–95 (2013); S Arimoto-Kobayashi, K Kaji, G M Sweetman, H Hayatsu, Mutation and formation of methyl- and hydroxylguanine adducts in DNA caused by N-nitrosodimethylamine and N-nitrosodiethylamine with UVA irradiation, Carcinogenesis 18(12):2429–2433 (1997); Becker K, Thomas AD, Kaina B, Does increase in DNA repair allow 'tolerance-to-insult' in chemical carcinogenesis? Skin tumor experiments with MGMT-overexpressing mice, Environ. Mol. Mutagen. 55(2):145-50 (2014).

[33] S Arimoto-Kobayashi, K Kaji, G M Sweetman, H Hayatsu, Mutation and formation of methyl- and hydroxylguanine adducts in DNA caused by N-nitrosodimethylamine and N-nitrosodiethylamine with UVA irradiation, Carcinogenesis 18(12):2429–2433 (1997).

[34] Verna L, Whysner J, Williams GM, N-nitrosodiethylamine mechanistic data and risk assessment: bioactivation, DNA-adduct formation, mutagenicity, and tumor initiation, Pharmacol. Ther. 71(1-2):57-81 (1996).

[35] Souliotis VL et al., Dosimetry of O6 methylguanine in rat DNA after low-dose, chronic exposure to Nnitrosodimethylamine (NDMA), Implications for the mechanism of NDMA hepatocarcinogenesis, Carcinogenesis, 16:2381±2387 (1995).

cytochrome enzyme P450 2E1 or "CYP2E1."[36] When left unrepaired, the O^6-methyl-guanine

can be mistakenly recognized as adenine, causing GC>AT substitution mutations during

replication, and misrecognition of O4-alkyl-thymidine can lead to TA>CG mutations.

Many chemicals (pro-carcinogens) require metabolic activation before becoming

genotoxic, and standard tissue culture techniques used during *in vitro* studies do not often

retain the metabolic capacity of the liver. Consequently, cell cultures use S9-fraction of liver

homogenate to provide an external metabolic capability. Recently, many cell lines used in

genetic toxicology have been engineered to express higher levels of metabolic enzymes (e.g.,

cytochrome P450s) and have been transfected with a virus or vector to introduce additional

enzymes. These cell lines (e.g., human lymphoblastoid cell line MCL-5, which is derived

from the AHH-1 cell line and transfected with metabolic enzymes) are thus metabolically

competent concerning the specific enzymes incorporated and are an alternative to adding S9-

fraction.

C. Dr. Panigrahy's single-dose theory is incorrect and unsupported by the literature.

Dr. Panigrahy's opinion that a "single dose" of NDMA or NDEA can be carcinogenic

is not correct in the context of the trace levels of NDMA/NDEA found in valsartan. At trace

levels like those found in valsartan, a single dose of NDMA/NDEA would be insufficient to

cause cancer. Dr. Panigrahy's single-dose opinion is further flawed because this 'one-hit'

theory does not apply to compounds like NDMA and NDEA that need to be metabolized in

order to become toxic, and where there is a clear DNA repair mechanism involved.

Another key discussion point is whether there are even suitable studies to show that a

single low dose of NDMA/NDEA induces or initiates cancer in multiple animal species, at

multiple sites, and in multiple strains of both male and female animals. There are no citations

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[36] Johnson, GE et al., Tolerability of risk - A commentary on the nitrosamine contamination issue, Journal of Pharmaceutical Sciences (2021).

included to support the "single dose" theory of Dr. Panigrahy, and we are therefore unable to

assess the precision of the statement through assessment of the study design cited.

Meanwhile, there is a wealth of excellent data in suitable systems with suitable study designs

for risk assessment purposes available, which has amassed since at least 1991 when Peto et

al. completed their cancer bioassay on NDMA and does not support Dr. Panigrahy's theory

that a single dose of NDMA/NDEA is sufficient to cause cancer, and particularly as it relates

to the trace amounts of NDMA/NDEA at issue here.

Dr. Panigrahy's statement around lifetime exposure to NDMA at 2,453µg and NDEA

at 677µg is accepted, but we do not accept that there is an accumulation of the compound

over a lifetime, due to metabolism, clearance and other homeostatic mechanisms. It is also

not accepted that there is accumulation of DNA and cellular damage that is equivalent to this

total dose provided in a single dose.

D. NDMA and NDEA have not been shown to activate the RAS oncogenes as a mechanism of tumour initiation.

Alkylating agents such as NDMA and NDEA are mutagens and tumour initiating

substances as described above. Some substances have mutation hotspots in certain cancer

genes such as the RAS family of oncogenes. However, I disagree with Dr. Panigahy's

opinion that NDMA and NDEA act on the RAS oncogene. As expanded upon below, there

are no robust or relevant studies to show that this is the case for NDMA or NDEA.

Researching this particular topic *in vitro* would also be very difficult, as prevalent mutagenic

adducts also occur endogenously and via food and environmental exposure, therefore a large

and well-designed study would be required in order to directly show this. Devereux 1991 is

the closest study, but has major flaws that preclude drawing any conclusive statement, as

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discussed more below.[37] Therefore, it is my opinion that NDMA and NDEA have not been

shown to be tumour promoting or initiating substances by the RAS oncogene, through the

evidence provided.

E. NDMA and NDEA are not tumour promotors.

Contrary to the description and opinion offered by Dr. Panigrahy and Dr. Lagana, the

science to date has not shown that NDMA and NDEA are 'tumour promotors' as that term is

commonly used. Tumour promotion is a process in which existing tumours are stimulated to

grow, and tumour promoters are not able to cause tumours to form.[38] NDMA and NDEA are

mutagenic compounds and, at certain concentrations and following metabolism, are able to

induce the first phase of tumour development, termed tumour initiation, under certain

conditions absent DNA repair. Tumour promotion is required in order to reach the next stage

of tumour development. This stage is characterised by the initiated cell's ability to survive

and have increased levels of cell division. A cell population can reach this stage, if the

substance to which they are exposed can target and decrease gene expression of specific

tumour suppressor genes, or increase gene expression of specific proto-oncogenes, then it

could be considered to have tumour promoting activity. Mutation spectrum analysis of

hotspots within these genes, or tailored assays including relevant gene expression or cell

transformation assays, can be used to assess for tumour promotion. I am yet to see any

convincing scientific publications which show that NDMA and NDEA are tumour promoters,

and the literature cited in the reports of Plaintiffs' experts do not support the conclusion that

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[37] Devereux TR, Anderson mW, Belinsky SA., Role of ras protooncogene activation in the formation of spontaneous and nitrosamine-induced lung tumors in the resistant C3H mouse, Carcinogenesis 12(2):299-303 (1991).
[38] NIH National Cancer Institute, NCI Dictionaries definition of "tumor promotion", https://www.cancer.gov/publications/dictionaries/cancer-terms/def/tumor-promotion (last accessed Aug. 1, 2021).

they are. Assays and approaches outlined in Jacobs et al. which assess the non-genotoxic

mechanisms that underlie tumour promotion were considered.[39]

Data would be required to show that the proposed mechanisms of tumour progression

in Dr. Lagana's report, including oxidative stress, inflammation, immunosuppression, and

angiogenesis, occur in the low dose region of NDMA and NDEA exposure. To date, these

have not been used in the regulatory risk assessments as this has not been a clear

characteristic of these substances in the relevant dose range associated in the animals, or the

human exposure levels. DNA alkylation and mutation have been well characterized in the

low dose region[40], but tumour promotion or progression has not.

F. Dr. Panigrahy's application of Haber's Rule does not apply to mutagenic toxicants with cancer bioassay data to support a non-linear threshold.

"Haber's Law simply states that the incidence and/or severity of a toxic effect

depends on the total exposure, i.e. exposure concentration (c) rate times the duration (t) of

exposure (c x t)."[41] Haber's rule of concentration x time = constant, is based on a linear

theory with regards to concentration and time. Dose fractionation studies elegantly showed

that this was not the case for a very comparable alkylating agent ENU/EMS known to have

similar mechanism as shown with NDMA/NDEA.[42] This study confirmed that if a dose is

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[39] Jacobs MN, Colacci A, Corvi R, Vaccari M, Aguila MC, Corvaro M, Delrue N, Desaulniers D, Ertych N, Jacobs A, Luijten M, Madia F, Nishikawa A, Ogawa K, Ohmori K, Paparella M, Sharma AK, Vasseur P, Chemical carcinogen safety testing: OECD expert group international consensus on the development of an integrated approach for the testing and assessment of chemical non-genotoxic carcinogens, Arch. Toxicol. 94(8):2899-2923 (2020).

[40] G.J.S. Jenkins, S.H. Doak, G.E. Johnson, E. Quick, E.M. Waters, J.M. Parry, Do dose response thresholds exist for genotoxic alkylating agents?, Mutagenesis, 20(6) 389–398 (2005); Gollapudi et al., Quantitative approaches for assessing dose–response relationships in genetic toxicology studies, Environmental and Molecular Mutagenesis Issue 1 (2013); Johnson, GE, et al., Derivation of Point of Departure (PoD) Estimates in Genetic Toxicology Studies and Their Potential Applications in Risk Assessment, Environmental and Molecular Mutagenesis (2014); Johnson, GE, et al., Permitted daily exposure limits for noteworthy N-nitrosamines, Environmental and Molecular Mutagenesis 62:293-305 (2021); Swenberg et al., 2010.

[41] Gaylor DW, The use of Haber's law in standard setting and risk assessment, Toxicology, 14;149(1):17-9 (2008).

[42] *See* Gocke E, Müller L, In vivo studies in the mouse to define a threshold for the genotoxicity of EMS and ENU, Mutation Research 678(2):101-107 (2009).

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split and delivered over a longer duration, DNA repair is able to repair certain levels of the

damage on a regular basis, and therefore there would be a lower level of mutation than if

delivered in a single high dose.

This same principle pushes against Dr. Panigrahy's theory that there is a cumulative

dose or fixed level effect with NDMA/NDEA in valsartan. There would not be accumulation

of chemicals such as NDMA and NDEA, mainly due to the DNA repair, metabolism and

clearance of these substances.

Haber's law is used in risk assessment to influence the uncertainty (safety) factor

when using short-term studies, but for NDMA and NDEA, lifetime cancer studies are used

and no additional adjustment for duration is required. Johnson et al. show that across 2, 4 and

8 weeks, NDEA had no influence on the position of the benchmark dose confidence interval

(BMD CI), which potentially means that Haber's Law could have less relevance for gene

mutation, where adducts and mutations do not increase with time as they take a shorter time

to manifest and standard length studies (e.g., 28 day) are sufficient for extrapolation to long

term human exposure. However, this is currently theoretical for gene mutation, and

experiments are currently being carried out in order to directly address this.

Statements around NDMA inducing the transformation of normal cells to cancer cells

are not supported by the data presented in the most comprehensive cancer bioassay published

in the Peto et al. 1991 study,[43] where numerous doses resulted in cancer incidence

comparable to the background levels of the control animals. Bilinear (e.g., broken stick,

segmented) modelling[44] to prove 'thresholds' for data sets such as Peto et al. cancer dose

response is not suitable, because there are underlying issues with the statistical model used in

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[43] Peto et al. 1991a; Peto, et al. 1991b.
[44] Johnson, GE, et al., Derivation of Point of Departure (PoD) Estimates in Genetic Toxicology
Studies and Their Potential Applications in Risk Assessment, Environmental and Molecular
Mutagenesis (2014).

that analysis (see **Figure 5** below). However, BMD modelling using a suite of nonlinear

models to calculate a BMD is suitable for these data sets, and has been carried out with high

precision.[45] To support this approach, a threshold mechanism linking a homeostatic

mechanism to the dose response is standard practice, and that has also been done for these

compounds.[46]

Thus, there is no evidence to support a single dose theory of NDMA/NDEA causing

cancer in humans by a one-time dose, at the levels of these impurities in the valsartan tablets.

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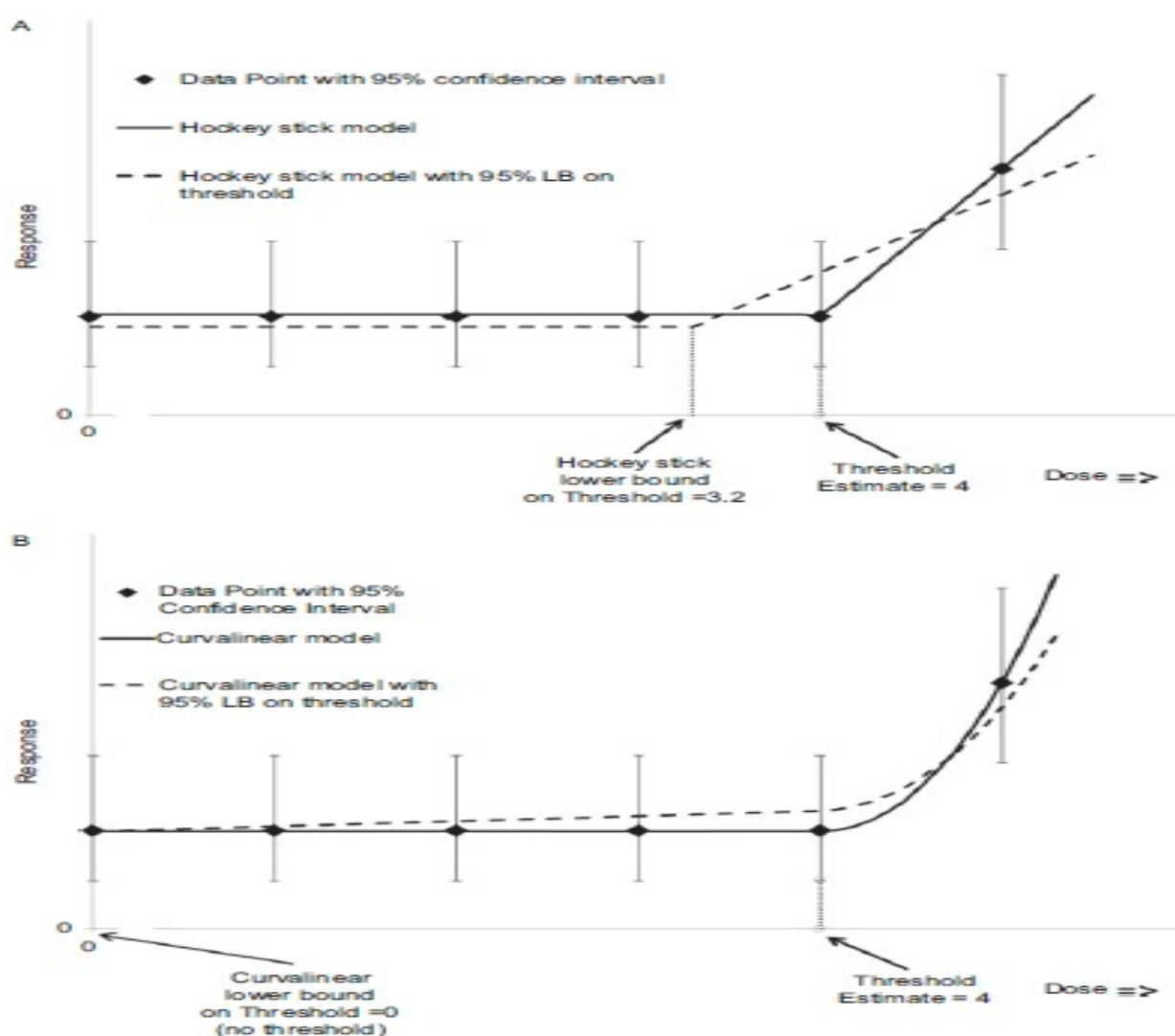
[45] EFSA Scientific Committee, Update: use of the benchmark dose approach in risk assessment
(2017), available at https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903 /j.efsa. 2017.4658.
[46] *See* Johnson, GE et al., Permitted daily exposure limits for noteworthy N-nitrosamines,
Environmental and Molecular Mutagenesis 62:293-305 (2021).

Figure 5: A threshold cannot be statistically bounded away from zero without specific and possibly implausible assumptions about the shape of the dose response. (A:) The hockey stick model provides a statistical lower bound for the threshold of 3.4 units. (B:) A curvilinear model describes the data as well as the hockey stick model but provides a statistical lower bound for the threshold of zero (i.e., no threshold).[47]

VIII. DNA Repair Mechanism Mitigates Mutagenicity from NDMA and NDEA and Restores DNA Integrity to Prevent Cancer.

It has been shown that DNA repair mechanism mitigates the induced DNA damage by NDMA and NDEA. Specifically, this was shown in a study where the DNA repair mechanism in MGMT was turned off and compared to the level of mutation caused by NDMA when it is left to act as it would in the body.[48] The results show no mutations when the MGMT is present, but when taken away the mutation level rises significantly.[49]

If mutation occurs from the NDMA/NDEA metabolites, the body recognizes that the DNA cannot replicate normally and there is an 'up activation' of the body's mechanisms for repairing DNA damage. MGMT removes the methyl or ethyl group that caused the DNA damage from O^6-alkyl-guanine or O4-alkyl-thymidine, leaving a normal guanine and thymine residue. The original integrity of the DNA is thus restored. MGMT's ability to remove base alkylations to restore the normal, natural DNA sequence represents an error-free DNA damage response that can mechanistically account for the manifestation of a dose-response threshold.[50]

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[47] Crump KS, Use of threshold and mode of action in risk assessment, Crit. Rev. Toxicol. 41(8):637-650 (2011).

[48] S Arimoto-Kobayashi, K Kaji, G M Sweetman, H Hayatsu, Mutation and formation of methyl- and hydroxylguanine adducts in DNA caused by N-nitrosodimethylamine and N-nitrosodiethylamine with UVA irradiation, Carcinogenesis 18(12):2429–2433 (1997).

[49] *Id.*

[50] *See* Kaina B, Fritz G, Mitra S, Coquerelle T, Transfection and expression of human O6-methylguanine-DNA methyltransferase (MGMT) cDNA in Chinese hamster cells: the role of MGMT in protection against the genotoxic effects of alkylating agents, Carcinogenesis 12:1857–1867 (1991); Kaina, B., Fritz, G. & Coquerelle, T, Contribution of O6-alkylguanine and N-alkylpurines to the formation of sister chromatid exchanges, chromosomal aberrations, and gene mutations: new insights gained from studies of genetically engineered mammalian cell lines, Environmental and Molecular Mutagenesis, 22(4):283–292 (1993); Margison, G.P., Povey, A.C., Kaina, B. & Santibanez Koref, M.F., Variability and regulation of O6-alkylguanine-DNA alkyltransferase, Carcinogenesis 24(4):625–635 (2003); Thomas, A.D., Jenkins, G.J., Kaina, B., Bodger, O.G., Tomaszowski, K.H.,

A. How cell cycle checkpoints help to maintain the genome

Regulation of the cell cycle is maintained via checkpoint pathways which control the order and timing of cell cycle transitions and ensure DNA replication and segregation are completed with high fidelity as they are crucial events. Moreover, checkpoints provide the capability for cell cycle arrest in response to damage, thus facilitating repair by providing time and inducing transcription of DNA repair genes.[51] As such, the loss or damage of a checkpoint can result in genomic instability which may lead to neoplasia (i.e., the formation of tumours).

DNA damage checkpoints employ damage sensor proteins to detect DNA damage and to initiate signal transduction cascades that induce Chk1 and Chk2 Ser/Thr kinases and Cdc25 phosphatases.[52] These signal transducers activate p53 and inactivate cyclin-dependent kinases which inhibits cell cycle progression from G_1 to S (the G_1/S checkpoint), DNA replication (the intra-S checkpoint), or G_2 to mitosis (the G_2/M checkpoint).[53]

The G_1 checkpoint is involved with ensuring there is adequate machinery for future events and accurate transmission of DNA.[54] Cells which have escaped the G_1 checkpoint and are genomically unstable are eliminated by the G_2 checkpoint via an apoptotic pathway.[55] The mitotic checkpoint is a signalling cascade that arrests the cell cycle in mitosis when even a single chromosome is not properly attached to the mitotic spindle.[56] Bypassing these cell

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Lewis, P.D. et al., Influence of DNA repair on nonlinear dose-responses for mutation, Toxicological Sciences 132(1), 87–95 (2013); Thomas AD, Fahrer J, Johnson GE, Kaina B, Theoretical Considerations for Thresholds in Chemical Carcinogenesis, Mutation Research - Reviews 765:56-67 (2015).

[51] Elledge SJ, Cell cycle checkpoints: preventing an identity crisis, Science 274(5293):1664-1672 (1996).

[52] Sancar A, Lindsey-Boltz LA, Unsal-Kacmaz K, Linn S, Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints, Annu Rev Biochem 73:39-85 (2004).

[53] *Id.*

[54] Elledge SJ, Cell cycle checkpoints: preventing an identity crisis, Science 274(5293):1664-1672 (1996).

[55] Piette J, Munoz P, Implication of the G2 checkpoint in the maintenance of genome integrity, Pathol Biol (Paris) 48(3):174-181 (2000).

[56] Kops, G., Weaver, B., Cleveland, D, On the road to cancer: aneuploidy and the mitotic checkpoint, Nat Rev Cancer 5:773–785 (2005).

cycle checkpoints could lead to cells with (i) aberrant mitotic machinery (G_1 checkpoint), (ii)

genomic instability that should be eliminated by apoptosis (G_2 checkpoint) and/or (iii)

chromosome and cell division aberrations (mitotic checkpoint). As a consequence, several

human heritable cancer-prone syndromes known to alter DNA stability have been shown to

have defects in these checkpoint surveillance pathways. Familial breast and ovarian

carcinoma syndrome are known to have a mutant allele in the *BRCA1* and *BRCA2* genes, and

as a consequence result in genomic instability where further mutations can arise to produce

neoplasia. The *BRCA1* protein contributes to cell-cycle arrest and DNA repair by

homologous recombination alongside many other functions, whereas another important

tumour suppressor gene, *p53,* controls genes involved in cell death and DNA-repair

mechanisms.[57]

B. The DNA repair process preserves DNA adduct integrity and prevents cancer from low-level exposure to NDMA/NDEA.

Over recent decades, DNA repair has been shown to function in a complex and, in

some cases, inducible manner to control the genetic stability of the host cell's genome.[58]

Several overlapping DNA repair pathways exist (e.g., Base Excision Repair, Nucleotide

Excision Repair, Homologous Recombination, Mismatch Repair, etc.), and each is

responsible for repairing specific DNA damage types (e.g., small and bulky adducts, DNA

strand breaks, and base mismatches). Hence, it is likely that DNA repair will impact directly

on the linearity of genotoxic dose responses by removing DNA damage towards a non-linear

response. This is particularly true at low doses of genotoxicant exposure, as DNA repair has

evolved to deal with constant low-level DNA damage induction. DNA repair may be

saturated where higher levels of mutations are observed and hence may not be able to remove

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[57] Kastan MB, Bartek J, Cell-cycle checkpoints and cancer, Nature 18:432 (7015):316-23 (2004).
[58] Ames BN, Shigenaga MK, Gold LS, DNA lesions, inducible DNA repair, and cell division: three key factors in mutagenesis and carcinogenesis, Environmental health perspectives 101 Suppl 5(Suppl 5):35-44 (1993).

newly damaged DNA bases. There is some evidence that DNA adduct formation accrues in a

linear fashion,[59] although recent evidence challenges this[60]. Nevertheless, it is likely that

fixed mutations (point mutations, chromosome mutations) will not follow linearity.

One complication with comparing the DNA adduct data to the mutation data (point

mutation or chromosome mutation) is that DNA adducts can be detected to a level which is 3

to 4 orders of magnitude more sensitive than that to which DNA mutations can currently be

measured. Furthermore, another complication with this comparison is that DNA mutations

(point mutations in particular) are detected in specific gene sequences (hprt, tk, lacZ, lac I,

etc.), whereas current DNA adduct measurements do not define the location of the adducts in

the genome. Given that cells have evolved efficient measures to keep gene coding sequences

damage free at the expense of non-coding regions,[61] it is not possible to currently say if DNA

adducts accrue in a linear fashion in the coding sequences, which form the basis for most

genotoxicity tests.

DNA repair proficiency has been shown to have a measurable and consistent effect on

the position of the Point of Departure (PoD), through repair of low levels of specific adducts

and mutations.[62] For many nitrosamine induced adducts, MGMT is the key DNA repair

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[59] Perera, F.P., The significance of DNA and protein adducts in human biomonitoring studies, Mutat. Res. 205, 255–269 (1988); Zito, R., Low doses and thresholds in genotoxicity: from theories to experiments, J. Exp. Clin. Cancer Res. 20, 315–325 (2001); Swenberg, J.A., Fryar-Tita, E., Jeong, Y., Boysen, G., Starr, T., Walker, V.E., Albertini, R.J., Biomarkers in toxicology and risk assessment: Informing critical doseresponse relationships, Chem. Res. Toxicol. 21, 253–265 (2008).
[60] Kraus, A., McKeague, M., Seiwert, N. et al. Immunological and mass spectrometry-based approaches to determine thresholds of the mutagenic DNA adduct O6-methylguanine in vivo, Arch Toxicol 93:559–572 (2019).
[61] Hanawalt PC, Transcription-coupled repair and human disease, Science 23:1957–1958 (1994).
[62] White, P.A., et al., Quantitative Interpretation of Genetic Toxicity Dose-Response Data for Risk Assessment and Regulatory Decision-Making: Current Status and Emerging Priorities, Environmental and Molecular Mutagenesis 61:66-83 (2020).

enzyme, which is known to have a background level of approximately 200 molecules per cell, and is also inducible in rats[63] but this is yet to be shown in human cells[64].

One of the first reports to comprehensively demonstrate that direct acting genotoxicants could exhibit PoD with threshold mechanisms for mutation induction and chromosome breakage *in vitro* focused on a set of four well known genotoxic and carcinogenic alkylating agents: methyl methanesulfonate ("MMS"), *N*-methyl-*N*-nitrosourea ("MNU"), ethyl methanesulfonate ("EMS") and *N*-ethyl-*N*-nitrosourea ("ENU").[65] Given that MMS and EMS were known carcinogens and were often used as positive controls in genotoxicity testing, this evidence clearly refuted the linear model, which was assumed to apply for all direct acting genotoxicants. This is further supported through the MNU and ENU PoD, and the elucidation of the DNA repair mechanism supporting this dose response. These potent alkylnitrosoureas were previously common positive experimental controls and are also considered super-mutagens. Therefore, clear PoDs, accompanied with an explanatory threshold mechanism (see **Table 2** below) for these substances are highly relevant when

[63] Kaina, B., Fritz, G. & Coquerelle, T, Contribution of O6-alkylguanine and N-alkylpurines to the formation of sister chromatid exchanges, chromosomal aberrations, and gene mutations: new insights gained from studies of genetically engineered mammalian cell lines, Environmental and Molecular Mutagenesis, 22(4):283–292 (1993); V L Souliotis, J H van Delft, M J Steenwinkel, R A Baan, S A Kyrtopoulos, DNA adducts, mutant frequencies and mutation spectra in lambda lacZ transgenic mice treated with N-nitrosodimethylamine., Carcinogenesis, 19(5)731–739 (1998).
[64] Fritz G, Kaina B., Stress factors affecting expression of O6-methylguanine-DNA methyltransferase mRNA in rat hepatoma cells, Biochim Biophys Acta 1171(1):35-40 (1992).
[65] Doak SH, Jenkins GJ, Johnson GE, Quick E, Parry EM, Parry JM, Mechanistic influences for mutation induction curves after exposure to DNA-reactive carcinogens, Cancer Res 67:3904–3911 (2007); Shareen H. Doak, Katja Brüsehafer, Ed Dudley, Emma Quick, George Johnson, Russell P. Newton, Gareth J.S. Jenkins, No-observed effect levels are associated with up-regulation of MGMT following MMS exposure, Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, 648(1–2):9-14 (2008); Johnson, GE, et al., Quantitative aspects of DNA reactive genotoxins assessed in vitro, Mutagenesis 25(6):56 (2010); Thomas, et al. 2013; Zair ZM, Jenkins GJ, Doak SH, Singh R, Brown K, Johnson GE, N-Methylpurine DNA Glycosylase Plays a Pivotal Role in the Threshold Response of Ethyl Methanesulfonate-Induced Chromosome Damage, Toxicological Sciences 119(2):346-358 (2011); Thomas AD, Fahrer J, Johnson GE, Kaina B, Theoretical Considerations for Thresholds in Chemical Carcinogenesis, Mutation Research - Reviews 765:56-67 (2015); Thomas AD, Jenkins GJ, Kaina B, Bodger OG, Tomaszowski KH, Lewis PD, Doak SH, Johnson GE. 2013. Influence of DNA repair on nonlinear dose-responses for mutation. Toxicol Sci 132(1):87-95 (2013).

considering how to risk assess potent genotoxic carcinogens, and that the default linear

approach may not always be suitable.

IX.   **Threshold Mechanisms of Mutagenic Carcinogens Have Been Well-Established to Calculate a Permissible Daily Exposure and Justify the Departure from the TD50 Linear Back-Extrapolation Approach.**

It is now known that carcinogenesis is a multifactorial process involving mutagenic

and non-mutagenic pathways and importantly the mutagenic "adverse outcome pathway" is

not linear, with molecular initiating events (adducts) and key events (mutations) being

repaired and/or simply not leading to a deleterious effect.[66] Furthermore, it is increasingly

accepted that threshold mechanisms exist for mutagenic carcinogens,[67] and an extensive

analysis of carcinogens has showed that "at non-toxic doses" thresholds exist for the

induction of experimental cancer for all types of genotoxic carcinogen, including NDMA[68].

Mechanistic information	Example(s)
Critical involvement of non-DNA targets	Aneuploidy: benomyl; carbendazim
Contribution of DNA repair mechanisms	Ethylmethane sulfonate
Detoxification capacity exceeded	Hydroquinone; paracetamol (acetaminophen)
Disruption of enzymes involved in DNA synthesis or replication	Topoisomerase II inhibitors; anti-metabolites; methotrexate
Chemical reactivity or properties unlikely to occur *in vivo*	Captan; trichloroacetic acid
Inadequate uptake or toxicokinetics limiting distribution to target	Chromium III
Mutational spectrum in tumor genes similar to those in untreated animals	Trichloroacetic acid
Structural similarities to similar threshold-acting chemical	Folpet; captan
Secondary or indirect origin of the observed damage	Oxidative damage; ethylene glycol monobutyl ether
Species and tumor-specific non-genotoxic mode of action	Induction of thyroid follicular cell tumors by inorganic chlorates

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[66] Yauk CL, Lambert IB, Meek ME, Douglas GR, Marchetti F, Development of the adverse outcome pathway "alkylation of DNA in male premeiotic germ cells leading to heritable mutations" using the OECD's users' handbook supplement, Environ Mol Mutagen (2015).

[67] MacGregor JT, Frötschl R, White PA, Crump KS, Eastmond DA, Fukushima S, Guérard M, Hayashi M, Soeteman-Hernandez LG, Johnson GE, Kasamatsu T, Levy D, Morita T, Müller L, Schoeny R, Schuler MJ, Thybaud V, IWGT Report on Quantitative Approaches to Genotoxicity Risk Assessment II: Use of Point-of-Departure (PoD) metrics in defining acceptable exposure limits and assessing human risk, Mutation Research - Genetic Toxicology 783:66-78 (2015); James T. MacGregor, Roland Frötschl, Paul A. White, Kenny S. Crump, David A. Eastmond, Shoji Fukushima, Melanie Guérard, Makoto Hayashi, Lya G. Soeteman-Hernández, Toshio Kasamatsu, Dan D. Levy, Takeshi Morita, Lutz Müller, Rita Schoeny, Maik J. Schuler, Véronique Thybaud, George E. Johnson, IWGT report on quantitative approaches to genotoxicity risk assessment I. Methods and metrics for defining exposure–response relationships and points of departure (PoDs), Mutation Research/Genetic Toxicology and Environmental Mutagenesis, Volume 783, 2015, Pages 55-65, ISSN 1383-5718.

[68] Kobets T, Williams GM, Review of the evidence for thresholds for DNA-Reactive and epigenetic experimental chemical carcinogens, Chem Biol Interact 301:88-111 (2019).

Table 2[69]**:** Examples of mechanistic information used by authoritative bodies to infer that a non-linear threshold-type dose response occurred or that genotoxicity/carcinogenicity did not occur through a mutagenic or human-relevant mode of action.

Terminology around the background levels of adducts and mutations must be clearly defined when using mutation data for risk assessment purposes. Endogenous sources of DNA damage are defined here as including reactive oxygen species, formaldehyde, as well as sources such as gut nitrosation and cellular metabolism. Exogenous sources can be divided into two distinct categories, which are from environmental exposures including food and water, or from drug-related factors including impurities. Endogenous damage is not fully considered with the linear approach (as shown in **Figure 6**).

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[69] McCarroll NE, Protzel A, Ioannou Y, Frank Stack HF, Jackson MA, Waters MD, Dearfield KL, A survey of EPA/OPP and open literature on selected pesticide chemicals III: Mutagenicity and carcinogenicity of benomyl and carbendazim, Mutat Res 512(1):1-35 (2002); CTF Captain Task Force, Scientific Analysis of the Data Relating to the Reclassification of Captan under EPAs new Guidelines for Carcinogen Risk Assessment, US EPA Docket OPP 2004-0296, 2004, 0034 (2004); EMA, Guideline on Limits of Genotoxic Impurities, EMEA/CHMP/QWP/251344 (2006); Gordon E. Captan: transition from 'B2' to 'not likely': How pesticide registrants affected the EPA Cancer Classification Update, J Appl Toxicol 27(5):519-526 (2007); European Medicines Agency, Studies Assessed by the European Medicines Agency IndicateNno Increased Risk of Developing Cancer for Patients who have taken Viracept Contaminated with Ethyl Mesilate, Press Release London, 24 July 2008, Doc. Ref. EMEA/CHMP/382256/2008, 2008, www.ema.europa.eu/docs/en GB/document library/Press release/2009/ 11/WC500015040.pdf; Straif K, Benbrahim-Tallaa L, Baan R, Grosse Y, Secretan B, Bouvard GFEV, Guha N, Freeman C, Galichet L, Cogliano V., A review of human carcinogens– part C: metals, arsenic, dusts, and fibres (2009); COM, Guidance Statement: Thresholds for In Vivo Mutagens In: Committee on Mutagenicity of Chemicals in Food CPatE, editor (2010); U.S. Environmental Protection Agency, Carcinogenicity assessment of ethylene glycol monobutyl ether, Integr. Risk Inf. Syst. (2010), http://www.epa. gov/iris/subst/0500.htm (accessed 09.17.14); U.S. Environmental Protection Agency. Assessment of thyroid follicular cell tumors, Publication EPA/630/R-97/002. http://www.epa.gov/raf/publications /thyroid-follicular-cell-tumor.htm (accessed 09.17.14); Captan Task Force, Scientific Analysis of the Data Relating to the Reclassification of Captan under EPAs new Guidelines for Carcinogen Risk Assessment, US EPA Docket OPP 2004-0296, 2004, 0034. http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2004-f0296-0034 (accessed 09.26.14); U.S. Environmental Protection Agency, Carcinogenicity assessment for trichloroacetic acid, Integr. Risk Inf. Syst. (2011), http://www.epa.gov/ iris/subst/0655.htm (accessed 09.17.14); Eastmond DA, Factors influencing mutagenic mode of action determinations of regulatory and advisory agencies. Mutat Res. (2012); Hayashi M, Honma M, Takahashi M, Horibe A, Tanaka J, Tsuchiya M, Morita T, Identification and evaluation of potentially genotoxic agricultural and food-related chemicals, Food Safety 1:32-42 (2013).
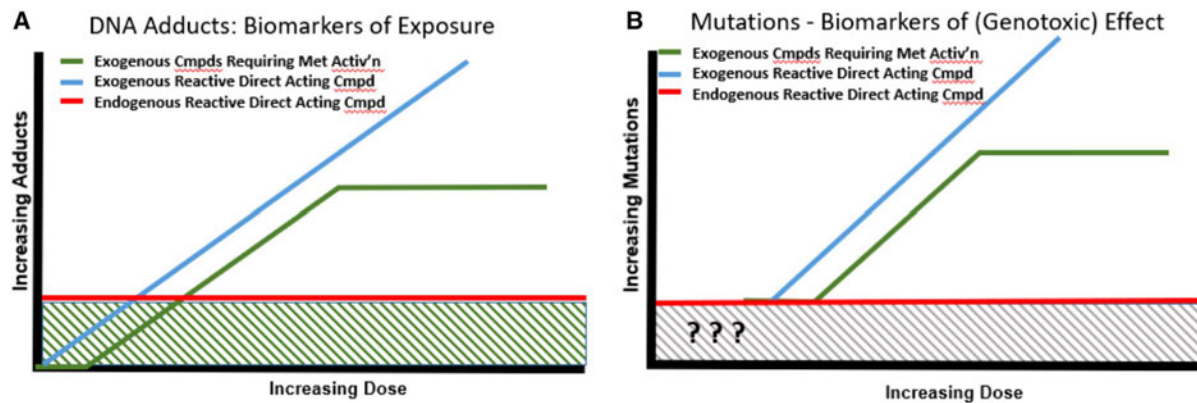
Figure 6. Schematic representation of theoretical dose-response curves for Biomarkers of (A) Exposure (DNA adducts) and (B) (Genotoxic) Effect (Mutations). Hashed regions represent background levels.[70]

X. Animal Studies of NDMA/NDEA Do Not Provide Evidence of Carcinogenicity in Humans at the Low Levels of NDMA/NDEA Found in Valsartan.

The expert reports offered by Plaintiffs have in common a general misconception of

the results of the animal studies cited in the reports. Any animal study where the exposure to

NDMA avoids the liver either by an IV or IP injection or by inhalation will not provide

reliable data on the carcinogenicity of the NDMA/NDEA found in finished dose tablets

which are orally ingested. Studies where the NDMA/NDEA is placed in the drinking water

of the lab animals likewise cannot be used to conclude NDMA/NDEA causes those cancers

in humans because there is exposure to the upper GI and GI tract without first being

metabolized by the liver.[71]

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[70] Pottenger LH, Boysen G, Brown K, Cadet J, Fuchs RP, Johnson GE, Swenberg JA, Understanding the importance of low-molecular weight (ethylene oxide- and propylene oxide-induced) DNA adducts and mutations in risk assessment: Insights from 15 years of research and collaborative discussions, Environ. Mol. Mutagen 60(2):100-121 (2019).

[71] *See, e.g.*, Anderson, LM, et al., Characterization of ethanol's enhancement of tumorigenesis by N-nitrosodimethylamine in mice, Carcinogenesis 13:2107-2111 (1992); Terracini, B, et al., The effects of long-term feeding of DDT to BALB/c mice, International Journal of Cancer 11:747-764 (1973); Lijinsky, W, et al., Dose response studies of carcinogenesis in rats by nitrosodiethylamine, Cancer Research 41:4997-5003 (1981); Lijinsky, W, et al., Carcinogenesis by combinations of N-nitroso compounds in rats, Food and Chemical Toxicology 21:601-605 (1983); Lijinsky, W, et al., Carcinogenesis in rats by nitrosodimethylamine and other nitrosomethylalkylamines at low doses, Cancer Letters 22:83-88 (1984); Berger, MR, et al., Combination experiments with very low doses of three genotoxic N-nitrosamines with similar organotropic carcinogenicity in rats, Carcinogenesis 8:1635-1643 (1987).

Additionally, there is a lot of emphasis on NDMA and NDEA having carcinogenic

potential in a wide range of organisms. There are extensive data in rodents, and these are used

as default for human health risk assessment, with non-human primates or other higher order

mammals being of relevance as well. The ecotoxicology and hazard identification approach

with lower order organisms, including frogs, is of little relevance to the current human health

risk assessment, where emphasis is placed on rodent models.[72] This comparison to

carcinogenicity in these varied species, at doses hundreds of times higher than those at issue

here and by means of exposure which avoid the primary mechanism of metabolism at issue

with ingested tablets of valsartan and the keen role of the liver in both metabolizing and

excreting NDMA, is not informative of the question of whether NDMA/NDEA at the low

levels in valsartan tablets are capable of causing cancer in humans. In my opinion, these

studies are inappropriate for use in such a risk assessment.

Furthermore, reports of direct comparisons of the responses of human cells and rodent

cells have revealed differences in sensitivities to experimental treatments. Human cells,

compared with rodent cells, have been found up to 1000 fold more sensitive to some

cytotoxic antibiotics, six times more sensitive to hydrogen peroxide and about twice as

sensitive to radiation.[73] However, when exposed to other substances, rodent cells are often

more sensitive than human cells which must be taken into consideration when designing a

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[72] *See* ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in
Pharmaceuticals to Limit Potential Carcinogenic Risk (March 2017); OECD, 451 Carcinogenicity
Studies, https://www.oecd.org/env/test-no-451-carcinogenicity-studies-9789264071186-en.htm
(2018).
[73] Gupta JB, Prasad K, Mechanism of H2O2-induced modulation of airway smooth muscle, Am J
Physiol 263(6 Pt 1):L714-722 (1992); Hoffmann ME, Mello-Filho AC, Meneghini R, Correlation
between cytotoxic effect of hydrogen peroxide and the yield of DNA strand breaks in cells of
different species, Biochim Biophys Acta 781(3):234-238 (1984); Cox R, Thacker J, Goodhead DT,
Inactivation and mutation of cultured mammalian cells by aluminium characteristic ultrasoft X-rays.
II. Dose-responses of Chinese hamster and human diploid cells to aluminium X-rays and radiations of
different LET, Int J Radiat Biol Relat Stud Phys Chem Med 31(6):561-576 (1977a); Cox R, Thacker
J, Goodhead DT, Munson RJ, Mutation and inactivation of mammalian cells by various ionising
radiations, Nature 267(5610):425-427 (1977b).

study. Certain human lymphoblastoid cell lines have enhanced levels of metabolising

enzymes, and AHH-1 TK$^{+/-}$ cells inducibly express CYP-1A1, and are sensitive to many

promutagens that are activated by this enzyme.[74] Subsequently, AHH-1 cells are sensitive to

the mutagenic action of both chemically reactive mutagens and mutagens which require

oxidative metabolism by the CYP-1A1 enzyme to exert their mutagenicity.[75] MCL-5 cells

were genetically modified AHH-1 cells, which include high levels of metabolic enzymes

including CYP-2E1.[76] Furthermore, the ability of metabolically competent cell lines

expressing cDNAs encoding the cytochrome P450 isoenzymes to metabolise halogenated

hydrocarbons to genotoxic species, including both clastogens and aneugens has been

demonstrated[77] and confirms that these cells are competent in oxidative xenobiotic

metabolism via a mixed-function oxygenase (MFO) activity. Therefore, numerous models are

available to assess the metabolism and genotoxicity of these substances in human relevant

systems, and less relevant test models should be avoided for assessing the risk of NDMA and

NDEA.

There are many types of toxicity tests performed on animals to gain an understanding

as to the cellular and tissue response to toxins. There are many factors that can affect the

outcome of a test or create uncertainty about its extrapolation to a heterogeneous human

population (e.g., genomic instability, DNA repair capacity, metabolic rate and exogenous

factors such as fitness and diet). However, by assessing responses to chemicals at the cellular

level, much can be discovered and extrapolation of these data to whole organisms is a great

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[74]   Woodruff NW, Durant JL, Donhoffner LL, Penman BW, Crespi CL, Human cell mutagenicity of chlorinated and unchlorinated water and the disinfection byproduct 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX), Mutat Res 495(1-2):157-168 (2001).

[75] Crespi CL, Thilly WG, Assay for gene mutation in a human lymphoblast line, AHH-1, competent for xenobiotic metabolism, Mutat Res 128(2):221-230 (1984).

[76] Johnson, GE, et al., Quantitative aspects of DNA reactive genotoxins assessed in vitro, Mutagenesis 25(6):56 (2010).

[77] Doherty AT, Ellard S, Parry EM, Parry JM, An investigation into the activation and deactivation of chlorinated hydrocarbons to genotoxins in metabolically competent human cells, Mutagenesis 11(3):247-274 (1996).

method for the hazard and risk assessment of genotoxicants, so there is value to the testing.

However, the conclusions offered by Dr. Panigrahy, Dr. Hecht and Dr. Lagana with regards

to many of the animal studies are out of scope of the current risk assessment of the potential

for carcinogenicity in humans.

A. Carcinogenic doses in humans cannot be directly extrapolated from animal studies because the metabolism and DNA repair is quantitatively different.

Dr. Hecht's report asserts that "Human metabolism of NDMA, NDEA, and other

nitrosamines by the pathways known to lead to DNA damage – **identical** to that seen in rats

that developed tumours upon treatment with these nitrosamine – has been demonstrated in

numerous studies using various experimental systems." I disagree with this statement. The

types of metabolic enzymes can be said to be identical. However, the levels of these enzymes

are not even identical (homogeneous) within the human population itself, and this variation

(heterogeneity) is also true across species as rat strains as well, hence the adjustment factors

are included in risk assessment to address this information.

Dr. Hecht goes on to discuss the types of adducts and mutations caused by NDMA

and NDEA; however, there is no information about the levels of these adducts, which renders

any discussion and conclusions meaningless.[78] This is particularly apparent in the statements

about these adducts and mutations being found in human tissue exposure to NDMA *in vitro*,

but as they are also formed endogenously (see **Table 3**), without this information on levels,

the statements become meaningless as these adducts and mutations would also be present in

the vehicle control.

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[78] There are endogenous mutagens formed every day in the body, which results in a certain number
(approximately 300) of the NDMA-specific mutation adducts in any given cell. Therefore, there is
perpetual DNA repair in process in the body on this specific adduct.

Steady-State Amounts of Selected endogenous DNA Damage	
Endogenous DNA lesions	Number per cell
Abasic sites	30,000
N7-(2-Hydroxyethyl)guanine (7HEG)	3000
8-Hydroxyguanine	2400
7-(2-Oxoethyl)guanine	1500
Formaldehyde adducts	960
Acrolein-deoxyguanosine	120
Malondialdehyde-deoxyguanosine	60
$N^2,3$-Ethenoguanine (ϵG)	36
$1,N^2$-Ethenodeoxyguanosine ($1,N^2$-ϵdG)	30
$1,N^6$-Ethenodeoxyadenosine ($1,N^6$-ϵdA)	12
Total	38,118

Table 3: Steady-state amounts of selected endogenous DNA damage.[79] Note that there are approximately 600 O^6-alkyl-guanine lesions per cells, from my personal calculations from Kraus et al..[80]

When we start discussing the levels of adducts and mutations along with DNA repair and metabolic enzymes instead of presence or absence of each of these, we are able to consider a refined risk assessment. A linear risk assessment approach bypasses the biology and implements an overly conservative and imprecise extrapolation and measurement of risk to the exposure human population. In addition to this, the route of exposure is a huge factor, particularly when the liver is the target organ, due to the increased levels of cytochrome P450 enzymes, therefore making certain routes of administration that bypass the liver obsolete and irrelevant for risk assessments for orally ingested tablets. Furthermore, the level of exposure

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[79] Swenberg, J. A., Lu, K., Moeller, B. C., Gao, L., Upton, P. B., Nakamura, J., & Starr, T. B. (2011). Endogenous versus exogenous DNA adducts: their role in carcinogenesis, epidemiology, and risk assessment. Toxicological sciences: an official journal of the Society of Toxicology, 120 Suppl 1 (Suppl 1), S130–S145.

[80] Kraus, A., McKeague, M., Seiwert, N. et al. Immunological and mass spectrometry-based approaches to determine thresholds of the mutagenic DNA adduct O6-methylguanine in vivo, Arch Toxicol 93:559–572 (2019); *see also* Pottenger LH, Boysen G, Brown K, Cadet J, Fuchs RP, Johnson GE, Swenberg JA, Understanding the importance of low-molecular weight (ethylene oxide- and propylene oxide-induced) DNA adducts and mutations in risk assessment: Insights from 15 years of research and collaborative discussions, Environ. Mol. Mutagen 60(2):100-121 (2019).

within the test animal species as well as in the humans is also of major importance. In Dr.

Hecht's report, he states that, "Given sufficient exposure to NDMA and NDEA, as with the

levels found in the contaminated valsartan . . . , the formation of these DNA adducts would

be sufficient to cause mutations and cancer in exposed humans," but he does not include any

references to support this statement. There is also no consideration of the PDE approach, at

which the levels in valsartan have not been proven to cause cancer in humans.

B. Tumours seen in animal studies are dependent on method of exposure and dose, and one cannot extrapolate every type of cancer seen in animal studies to humans.

In the report from Dr. Lagana, White et al.[81] was cited for the proposition that NDMA

activates certain RAS oncogenes as an alternative method of carcinogenesis. However, this

publication by Dr. White did not contain the original data, but instead cited to older data in

prior studies[82]. These prior studies also did not contain the original data, with Pottegard et al.

citing Tricker et al., and neither of these containing the original data but extrapolating a

general statement about nitrosamines inducing K-RAS mutations mainly through G>T

transitions in a paper by Bos,[83] whereas NDMA and NDEA are known to induce a G>A

transitions. The Bos 1988 paper shows different mutation spectra at the RAS gene family that

are associated with different cancers, but there are no data to link any specific nitrosamines,

including NDMA and NDEA, to RAS gene family mutations. The Devereux et al. paper[84]

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[81] White, P.A., et al., Quantitative Interpretation of Genetic Toxicity Dose-Response Data for Risk Assessment and Regulatory Decision-Making: Current Status and Emerging Priorities, Environmental and Molecular Mutagenesis 61:66-83 (2020).

[82] Tricker AR, Preussmann R, Carcinogenic N-nitrosamines in the diet: occurrence, formation, mechanisms and carcinogenic potential, Mutation Research/Genetic Toxicology 259(3):277-289 (1991); Liteplo, RG, et al. (WHO), Concise International Chemical Assessment Document 38: N-nitrosodimethylamine, IPCS Concise International Chemical Assessment Documents (2002); Pottegard A, et al., Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study (2018).

[83] Bos JL, The ras gene family and human carcinogenesis. Mutation Research/Reviews in Genetic Toxicology 195(3):255-271 (1988).

[84] Devereux TR, Anderson mW, Belinsky SA., Role of ras protooncogene activation in the formation of spontaneous and nitrosamine-induced lung tumors in the resistant C3H mouse, Carcinogenesis 12(2):299-303 (1991).

cited within the Literplo et al. paper,[85] did contain some relevant data, and is explored in the

section below. Therefore, each statement around NDMA inducing the k-RAS gene is based

on this problematic Devereux et al. study and is not a robust statement due to the issues

outlined below.

The citation Dr. Lagana relies upon to support NDMA's activation of the RAS family

oncogene did not take us to the original research, suggesting a lack of critique of the study

itself, and acceptance without question of the original findings in Devereux et al.. The

Devereux et al. study used a very high dose (3mg/kg, 7 weeks [3 times/week])

intraperitoneal injection. Seven spontaneous lung tumours were sequenced, to observe

activation of the K-RAS gene, and eleven tumours from NDMA treated were analysed. A

major issue with the study was that multiple tumours were often pooled from a single lung

from the NDMA treated animals, but not from the control animals. Note that 40% of the 7

spontaneous single (not pooled) lung tumours analysed contained an activated K-RAS gene,

therefore pooling the tumours in the controls as well, and could also result in 100% mutation

in the activated K-RAS gene for each vehicle control. Pooling tumours from NDMA-treated

animals could therefore mask un-activated genes in other tumours, to greatly bias the

mutation spectrum for NDMA treated tumours towards tumours that did contain the GC>AT

mutation within the K-RAS gene. Furthermore, this study does not contain sufficient

statistical power to provide robust results for mutation spectrum analysis, usually n=40 or

more. The single dose of 3mg/kg was higher than the top dose used in the most extensive and

robust NDMA cancer study (Peto et al.[86]) of 0.697mg/kg (male) and 1.224mg/kg (female),

and is far above the BMD CI of 0.062mg/kg and 0.107mg/kg calculated from Johnson et

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[85] Liteplo, RG, et al. (WHO), Concise International Chemical Assessment Document 38: N-nitrosodimethylamine, IPCS Concise International Chemical Assessment Documents (2002).
[86] Peto R, Gray R, Brantom P, Grasso P, Dose and time relationships for tumor induction in the liver and esophagus of 4080 inbred rats by chronic ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine, Cancer Res. 51(23 Pt 2):6452-69. PMID: 1933907 (1991).

al.[87]. Intraperitoneal route of administration bypasses first-pass metabolism from the gut, and also could avoid first-pass metabolism by the liver.

The studies cited by Dr. Lagana can be explained because of the non-ingestion routes of exposure. Substances administered through I.P injection enter the liver through the surface, and not via the hepatic portal vein, and the metabolism is very different through these two very different routes,[88] hence the reduced level or absence of mutations and tumours in the liver in I.P studies. Lung is also not the target organ for NDMA, as shown by the extensive number of cancer bioassays carried out on this compound, and as assessed by the regulatory bodies when deriving human exposure limits. This is likely due to I.P dosing bypassing metabolism in the gut and through the liver in the natural way, which would massively reduce the amount of NDMA and NDMA metabolites that would reach organs downstream of the liver, such as the lung.

Therefore, conclusions based on the data in Devereux et al. 1991 stating that NDMA is a tumour promoter are not valid, particularly when dose, route of exposure and tissues are considered in the exposed human population. From my analysis, I am yet to see a statement in current regulatory documents from FDA and EMA on NDMA and NDEA activating the RAS family. The RAS mechanism is the focus of Plaintiffs' experts' statements around NDMA and NDEA being tumour promoting agents. Therefore, this argument is based on very weak data, and I do not agree that NDMA and NDEA have been shown to be tumour promoters.

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[87] Johnson, GE, et al., Permitted daily exposure limits for noteworthy N-nitrosamines, Environmental and Molecular Mutagenesis 62:293-305 (2021).

[88] David Kirkland, Yoshifumi Uno, Mirjam Luijten, Carol Beevers, Jan van Benthem, Brian Burlinson, Stephen Dertinger, George R. Douglas, Shuichi Hamada, Katsuyoshi Horibata, David P. Lovell, Mugimane Manjanatha, Hans-Joerg Martus, Nan Mei, Takeshi Morita, Wakako Ohyama, Andrew Williams, In vivo genotoxicity testing strategies: Report from the 7th International workshop on genotoxicity testing (IWGT), Mutation Research/Genetic Toxicology and Environmental Mutagenesis, Volume 847, 403035 (2019).

XI.   **Assessing the Health Impact of Low Levels of Mutagenic Impurities on Humans**

Risk assessments can be performed on mutagenic impurities in a number of ways to estimate the risk level, if any, from exposure to specific levels of the impurities like NDMA and NDEA. Mutagenic impurities can be assessed in three main ways:

1. Linear extrapolation from the TD50 of available carcinogenicity data.

2. Using the threshold of toxicological concern ("TTC") concept.

3. ICH Q3C/M7: "permitted daily exposure" (PDE) using the BMD approach if there is sufficient evidence for a "practical threshold."

A. **Linear extrapolation from the TD50 of available carcinogenicity data to calculate an acceptable intake (AI) does not establish a risk of cancer above that level.**

As noted previously in this report, there are numerous problems with relying on the TD50 method to draw any conclusions on whether a compound causes cancer in humans. First, the TD50 method does not use confidence intervals, and as the uncertainty in a cancer risk estimate may be huge, this makes using a single value estimate for cancer risk meaningless.[89] So, if you have a poor study and a good study, both will be used. I also note that the TD50 method is not needed where, as with NDMA and NDEA, we are fortunate to have a 'mega-study' (rodent carcinogenicity bioassay[90]) in that an extended dose range was tested, with an increased number of replicates per dose (15 doses plus control at n=60).

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[89] Slob W. 2014a. Benchmark dose and the three Rs. Part I. Getting more information from the same number of animals. Critical Reviews in Toxicology 44(7):557-567; Slob W. 2014b. Benchmark dose and the three Rs. Part II. Consequences for study design and animal use. Critical reviews in toxicology 44(7):568-580.
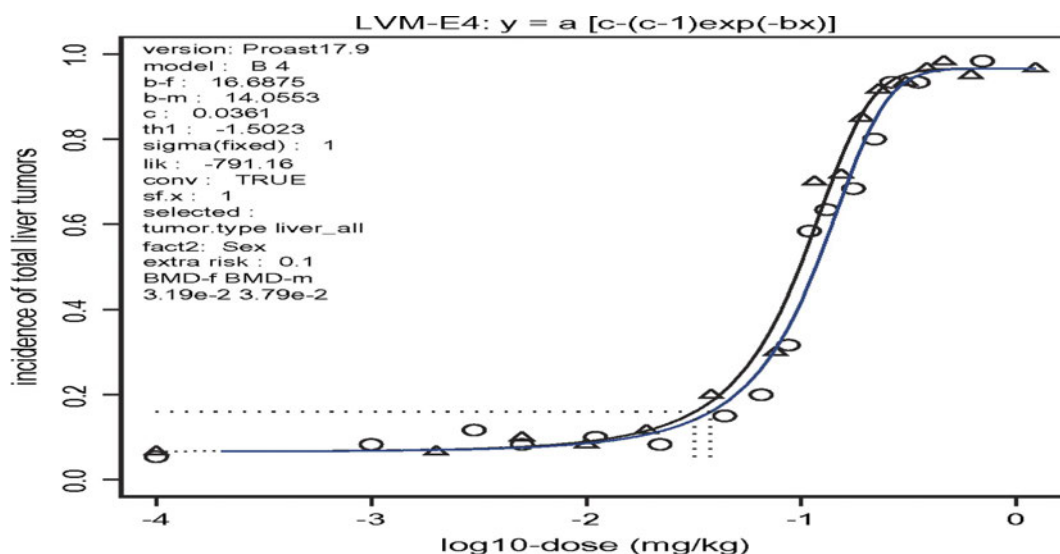[90] Peto et al. 1991a; Peto et al. 1991b.

Figure 7: Dose-response relationship for total liver tumours after lifelong exposure to NDMA via lifelong exposure to drinking water.[91] This is another study demonstrating the non-linear threshold for NDMA mutagenicity. Figure 7 shows data from Peto et al. (1991), with triangle indicating female and circle indicating male. The horizontal dotted line indicates the 10% extra risk level (compared with the estimated background response of 7.3%), and the two vertical dotted lines show associated doses (BMDs) for females and males.[92]

Figure 7 does not show that NDMA shows a clear linear dose response for cancer. Although regulatory authorities historically use the linear extrapolation approach from the TD50 values in animal studies to calculate an Acceptable Intake (AI) level to ensure the safety of a population exposed to a DNA-reactive carcinogen, its application for compounds such as NDMA and NDEA does not acknowledge the fundamental scientific shift in the quantitative approaches now advocated for regulatory interpretation of mutagenicity dose-response data.[93] This would include the Benchmark Dose (BMD) approach.

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[91] Marco J. Zeilmaker, Martine I. Bakker, Ronald Schothorst, Wout Slob, Risk Assessment of N-nitrosodimethylamine Formed Endogenously after Fish-with-Vegetable Meals, Toxicological Sciences, Volume 116, Issue 1, Pages 323–335 (2010).

[92] *Id.*

[93] Heflich RH, Johnson GE, Zeller A, Marchetti F, Douglas GR, Witt KL, Gollapudi BB, White PA, Mutation as a toxicological endpoint for regulatory decision-making, Environmental and Molecular Mutagenesis 61(1):34-41 (2020); White, P.A., et al., Quantitative Interpretation of Genetic Toxicity Dose-Response Data for Risk Assessment and Regulatory Decision-Making: Current Status and Emerging Priorities, Environmental and Molecular Mutagenesis 61:66-83 (2020).

1. FDA calculated an acceptable daily exposure limit for NDMA using the linear TD50 approach based only on rodent data.

The risk assessments for NDMA and NDEA by FDA to date have been based on the default linear-extrapolation approach of the cancer potency data to calculate an Acceptable Intake ("AI").[94] It should be noted that an AI is not intended to be a line above which cancer will occur – in other words FDA is not saying above 96 ng that NDMA causes cancer. To calculate a lifetime acceptable intake (AI) on which to base limits for these nitrosamines in pharmaceuticals, assuming a theoretical excess cancer incidence of 1 per 100,000, EMA's linear low-dose extrapolation from the TD50 yielded AI values of 96 ng/person/day for NDMA and 26.5 ng/person/day for NDEA.[95] The estimates represent extremely conservative AI values for human risk assessment, as they do not consider the full character of the dose-response relationship. These AI values are also being used as interim general limits for other nitrosamine impurities that lack carcinogenicity data to calculate compound-specific limits[96]. Furthermore, a stricter limit of 0.03 ppm supersedes AIs, based on technical feasibility of the analytical methods.[97] Not all N-nitrosamines are high-potency mutagenic carcinogens, based on their harmonic-mean TD50 values including ones with low and negligible potency.[98] Furthermore, based on the Lhasa data, nearly 20% of nitrosamines appear to be

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[94] Teasdale A, Urquart M, Organic Process Research & Development (2021).
[95] EMA, Nitrosamine impurities in human medicinal products, Article 5(3) of Regulation EC (No) 726/2004 (2020b).
[96] EMA, Lessons learnt from presence of N-nitrosamine impurities in sartan medicines, EMA/526934/2019 (2020a); EMA, Nitrosamine impurities in human medicinal products, Article 5(3) of Regulation EC (No) 726/2004 (2020b); Elder DP, Johnson GE, Snodin DJ. Tolerability of risk: A commentary on the nitrosamine contamination issue. J Pharm Sci. 2021 Jun;110(6):2311-2328. doi: 10.1016/j.xphs.2021.02.028. Epub 2021 Mar 9. PMID: 33705731.
[97] EMA, Lessons learnt from presence of N-nitrosamine impurities in sartan medicines, EMA/526934/2019 (2020a); EMA, Nitrosamine impurities in human medicinal products, Article 5(3) of Regulation EC (No) 726/2004 (2020b); Elder et al. 2021.
[98] Bercu JP, Hoffman WP, Lee C, Ness DK. Quantitative assessment of cumulative carcinogenic risk for multiple genotoxic impurities in a new drug substance. Regul Toxicol Pharmacol. 2008 Aug;51(3):270-7. doi: 10.1016/j.yrtph.2008.04.011. Epub 2008 Apr 27. PMID: 18550240.

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noncarcinogenic in rodent bioassays.[99] Therefore, N-nitrosamine carcinogenic potency

should be evaluated case by case, rather than assuming that all are of high potency based on

perceptions of the Cohort of Concern.

2. The descriptions of the TD50 analysis method and the conclusions reached by Dr. Etminan and Dr. Lagana are not accurate or reliable.

Dr. Etminan's description of the TD50 calculation and meaning is inaccurate in a

number of ways. In addition to the biological issues with his assumptions, there are also

several deficiencies observed when applying the linear extrapolation approach as FDA has

done with NDMA/NDEA, although it is a pragmatic approach for estimating de minimis risk

of mutagenic carcinogens. First, and perhaps the biggest concern with using TD50 data, is

that the default replicate number in a cancer bioassay used to determine the TD50 value is

limited to 50 animals per dose group per sex, and the number of tumours may be small. Thus,

extrapolating from the TD50 potency estimate to a dose theoretically associated with a cancer

risk of 1 in 100,000 or 1 in 1,000,000 conflicts with the statistical power of standard study

design, and it does not consider the substantial errors associated with the estimate of the

TD50. Second, adjustment factors are not included in the linear extrapolation, meaning that

the resulting excess cancer risk relates to the test species population and not the human

population. Third, confidence intervals (CIs) are not used, and as the uncertainty in a cancer

risk estimate may be huge, single value estimates of cancer risk are essentially meaningless

since they do not account for innate biological variation.[100]

FDA's TD50 risk assessment was also discussed in Dr. Panigrahy's report, but with

some additional critical mistakes and some basic misunderstanding. The TD50 is not a 10%

cancer incidence in rodents which would be in the low dose region of the dose response, but

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[99] Thresher A, Foster R, Ponting DJ, Stalford SA, Tennant RE, Thomas R, Are all nitrosamines concerning? A review of mutagenicity and carcinogenicity data, Regul Toxicol Pharmacol 116:104749 (2020).
[100] Slob 2014a; Slob 2014b.

50% cancer incidence, which is at the very high dose region of the dose response. This is a dramatic difference, and central to why the TD50 and an extrapolation from this high dose using a linear model does not include information in this lower dose region. It is my opinion that a 10% cancer incidence, as assessed using the Benchmark Dose approach with a benchmark response (BMR) of 10%, is a more precise and biologically relevant point of the dose response from which to carry out the risk assessment. Additionally, Dr. Panigrahy discusses TD50 as the median toxic dose, which is incorrect. ICH and FDA definitions around the TD50 do not mention toxicity. The following definition is from ICH M7 (R1) (2018): 'the dose giving a 50% tumour incidence (TD50),' where the 'most sensitive species and most sensitive site of tumour induction' are used.[101] Furthermore, 'when more than one study exists, the cancer potency database (CPDB) provides a calculated harmonic TD50,'[102] and these were what was used for NDMA and NDEA for calculation of the published Acceptable Intake (AI) values.

Interestingly, when the Committee for Medicinal Products for Human Use ("CHMP") Safety Working Party ("SWP") reviewed the issue of safe levels for the N-nitrosamines in November 2018, they were initially divided.[103] Many committee members (the *risk minimization sub-group*) thought that control of N-nitrosamines could be approached in a similar manner to any other mutagenic impurity, based on the extremely conservative approaches already utilized in ICHM7(R1).[104] There was no particular evidence that NDMA and NDEA were "fundamentally different from other mutagenic carcinogens, which are covered by the TTC framework in ICH M7(R1), besides being more potent."[105] This

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[101] ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (2018).
[102] *Id.*
[103] EMA, Assessment Report: Referral under Article 31 of Directive 2001/83/EC: Angiotensin-II-receptor antagonists (sartans) containing a tetrazole group, EMA/217823/2019 (2019).
[104] ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (March 2017).
[105] *Id.*

increased toxicity can be evaluated by "defining compound-specific thresholds based on

carcinogenicity data and by linear extrapolation" resulting in an AI– the strategy subsequently

adopted for the conservative interim limits.[106] As such, there is no requirement for a "no

threshold" approach. However, the more conservative part of SWP (the *risk avoidance sub-*

group) deemed that "there is no need to establish AIs for impurities in the first place as the

contamination risk is considered to be avoidable by avoiding certain manufacturing

processes."[107] However, as ongoing reform of the "Delaney Clause" in the US highlighted,[108]

total avoidance or absence of any contaminant is totally impracticable [109], and as regulatory

agencies have come to realize this, they have needed to put in place limits to control N-

nitrosamines in medicinal products. However, rather than continue to use the interim AIs,

they have implemented methodology-based limits that are entirely driven by analytical

capability and unrelated to classical safety-based limits – a clear case of agencies overly

conservative approach (see N-nitrosamines methodology).

B. Threshold of Toxicological Concern (TTC) does not consider human data and therefore cannot be relied upon to prove human carcinogenicity.

A TTC approach, originally based on food safety considerations, was developed to

describe an Acceptable Intake (AI) for any novel impurity. This equates to a generic

allowable exposure of 1.5 µg/day based on a carcinogenic risk of 1 in 100,000, which is

viewed as a virtually safe dose. The control strategies for impurities are based on established

risk-assessment approaches.

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[106] Johnson, GE et al., Tolerability of risk - A commentary on the nitrosamine contamination issue, Journal of Pharmaceutical Sciences (2021).

[107] EMA, Assessment Report: Referral under Article 31 of Directive 2001/83/EC: Angiotensin-II-receptor antagonists (sartans) containing a tetrazole group, EMA/217823/2019 (2019).

[108] Merrill RA, Food safety regulation: Reforming the Delaney Clause, Annu Rev Public Health (18):313-340 (1997).

[109] Elder D, Teasdale A, Is avoidance of genotoxic intermediates/impurities tenable for complex, multistep syntheses? Org Proc Res Dev (19):1437-1446 (2015).

The acceptable excess risk of carcinogenic potential is considered greater for early development phases, i.e. 1 in 1,000,000, because the acceptable risk in healthy human volunteers is lower than that in patients, although the total exposure duration is limited, i.e. less than lifetime ("LTL").[110] Thus, for example, if the acceptable intake (AI) is 1.5 µg/day for lifetime exposure, the LTL limits can be increased to a daily intake of 120 µg (< 1 month), 20 µg (> 1-12 months) or 10 µg (> 1-10 years' treatment duration). These LTL limits are applicable to both clinical development and for commercial products. In the latter case, ICH M7(R1) provides guidance in note 7 on those drug classes that can in theory utilize LTL limits.[111] For example, the 120 µg/day limit for treatment duration of < 1 month can be used for those drugs used in "emergency procedures (antidotes, anesthesia, acute ischemic stroke), actinic keratosis, and the treatment of lice."[112] In contrast, for commercial products, the lower cancer risk level of 1 in 100,000 is considered acceptable for lifetime exposure, i.e. 70 years. The LTL limits are applied to the AI within these guidelines, but there could be some consideration around applying these LTL corrections to the PDE as well.

The TTC was developed by the FDA as a 'threshold of regulation' for food contact materials[113] by the Center for Food Safety and Nutrition. It was derived by simple linear extrapolation from the carcinogenic potencies, measured as the dose giving a 50% tumour incidence (TD50) of more than 700 carcinogens. The methods and assumptions used to derive the TTC were conservative, using TD50 data from the most sensitive species and sites.

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[110] Joel P. Bercu, Melisa Masuda-Herrera, George Johnson, Andreas Czich, Susanne Glowienke, Michelle Kenyon, Rob Thomas, David J. Ponting, Angela White, Kevin Cross, Fernanda Waechter, Maria Augusta C. Rodrigues, Use of less-than-lifetime (LTL) durational limits for nitrosamines: Case study of N-Nitrosodiethylamine (NDEA), Regulatory Toxicology and Pharmacology, Volume 123, 2021.

[111] ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (March 2017).

[112] Id.

[113] Rulis AM. 1987. De minimis and threshold of regulation. In: Food Protection Technology, Proceedings of the 1986 Conference for Food Protection. C.W. Felix, ed. Lewis Publishers, Chelsea. pp 29-37.

A TTC figure of 1.5 µg/day was associated with a 1 in 10^6 lifetime cancer risk and was

termed a virtually safe dose (VSD) for any chemical, even if it should later prove to be a

carcinogen.[114] In the evaluation by Kroes et al. (2004) for mutagens/alerting structures and

their tumourigenicity, a TTC of 0.15 µg/day was associated with a 1 in 10^6 lifetime excess

cancer risk.[115] For pharmaceuticals, a higher limit of 1.5 µg/day, giving a 1 in 10^5 lifetime

risk, is considered acceptable, as there is a benefit associated with their intake, exposure is

intentional, and use is infrequently for a lifetime.[116] This remains a highly conservative

number given the high lifetime risk of cancer in the population at large.[117]

The staged TTC is based on knowledge about tumourigenic potency of a wide range

of genotoxic carcinogens and can be used for genotoxic compounds, for which cancer data

are limited or not available. The delineated acceptable daily intake values of between 1.5

µg/day for lifetime intake and 120 µg/day for 61 months are virtually safe doses. Based on

sound scientific reasoning, these virtually safe intake values do not pose an unacceptable risk

to either human volunteers or patients at any stage of clinical development and marketing of a

pharmaceutical product. The intake levels are estimated to give an excess cancer risk of 1 in

100,000 to 1 in a million over a lifetime, and are extremely conservative given the current

lifetime cancer risk in the population of over 1 in 4.[118]

C. **The Benchmark Dose (BMD) approach for mutagenic impurities with evidence for a practical threshold can be used to determine a Permitted Daily Exposure (PDE).**

The benchmark dose modelling approach, leading to a determination of an appropriate

PoD, is considered a more realistic starting point for excess cancer risk assessments than the

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[114] Rulis, 1987.

[115] Kroes, R, et al., Study on the carcinogenicity of lead arsenate and sodium arsenate and on the possible synergistic effect of diethylnitrosamine, Food and Cosmetics Toxicology 12:671-679 (1974).

[116] Müller L, et al., A rationale for determining, testing, and controlling specific impurities in pharmaceuticals that possess potential for genotoxicity, Regul Toxicol Pharmacol 44(3): 198-211 (2006).

[117] *Id.*

[118] *Id.*

methodology using linear extrapolation of the dose that results in a 50% increased tumour

incidence over background (TD50).[119] The latter approach assumes a straight line from the

TD50 to the background cancer frequency at zero dose, and is considered to be more

conservative and therefore tends to overestimate the real risk.

The BMD approach is a recognized alternative to the linear low-dose extrapolation

approach based on rodent carcinogenic potency (e.g., TD50) currently applied by FDA to

NDMA and NDEA based on the use of quantitative interpretation of in vivo mutagenicity

dose-response data for risk assessment and regulatory decision-making.[120] The TD50

approach is particularly relevant for other impurities, where carcinogenicity data are

unavailable or of poor quality for dose response analysis, but that is not the case here since

we have the Peto et al., 1991 cancer bioassay.[121] Peto et al. provides existing in vivo

mutagenicity dose-response data that display a mechanistically understood response

threshold.[122] More specifically, quantitative analyses of in vivo mutagenicity dose-response

data like what is found in Peto et al. can be used to determine a dose below which the

likelihood of a response at a key event along the "Adverse Outcome Pathway" (AOP)

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[119] ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (March 2017).

[120] Gollapudi et al., Quantitative approaches for assessing dose–response relationships in genetic toxicology studies, Environmental and Molecular Mutagenesis Issue 1 (2013); Johnson, GE, et al., Derivation of Point of Departure (PoD) Estimates in Genetic Toxicology Studies and Their Potential Applications in Risk Assessment, Environmental and Molecular Mutagenesis (2014); Benford DJ, The use of dose-response data in a margin of exposure approach to carcinogenic risk assessment for genotoxic chemicals in food, Mutagenesis 31(3):329-331 (2015); Labash C, Avlasevich SL, Carlson K, Berg A, Torous DK, Bryce SM, Bemis JC, MacGregor JT, Dertinger SD, Mouse Pig-a and micronucleus assays respond to N-ethyl-N-nitrosourea, benzo[a]pyrene, and ethyl carbamate, but not pyrene or methyl carbamate. Environ Mol Mutagen (2015); MacGregor et al. 2015a; White PA, Johnson GE, Genetic toxicology at the crossroads-from qualitative hazard evaluation to quantitative risk assessment, Mutagenesis 31(3):233-7 (2016); Heflich RH, Johnson GE, Zeller A, Marchetti F, Douglas GR, Witt KL, Gollapudi BB, White PA, Mutation as a toxicological endpoint for regulatory decision-making, Environmental and Molecular Mutagenesis 61(1):34-41 (2020); White, P.A., et al., Quantitative Interpretation of Genetic Toxicity Dose-Response Data for Risk Assessment and Regulatory Decision-Making: Current Status and Emerging Priorities, Environmental and Molecular Mutagenesis 61:66-83 (2020).

[121] Peto et al. 1991a; Peto et al. 1991b.

[122] Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM), Statement on the quantitative approaches to the assessment of genotoxicity data (2018).

(illustrated in **Figure 8**) in the test animal is negligible (i.e., a point of departure (PoD) such

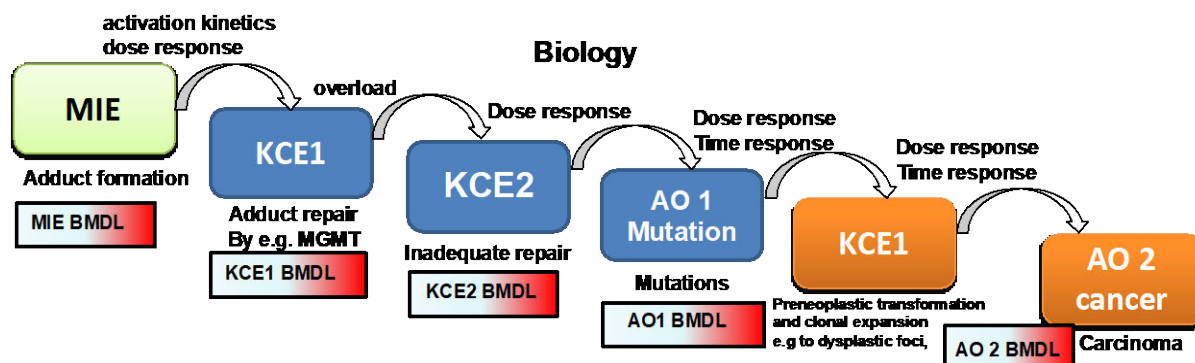as the no observed effect level ("NOEL"), threshold dose (Td), or benchmark dose (BMD)).

Figure 8: Adverse outcome pathway proposal from Roland Frotschl (GUM presentation 2021).

1. Using Health Based Guidance Values, i.e. uncertainty assumptions, provides a human based, practical basis for a BMD risk assessment.

The BMD approach can be used in risk assessment for humans through use of

uncertainty factors ("UFs"), that can be used to determine a regulatory human exposure limit.

UFs are also sometimes referred to as extrapolation or adjustment factors[123] of uncertainty or

modifying factors[124] metrics such as the NOEL or BMD, which are indicative of compound

potency. The recent article I co-authored with Dr. White reveals how this approach may be

applied to compounds like NDMA and NDEA where there is data available to determine

threshold levels and dose responses.[125] Specifically, we found that the adjustment factors are

suitable for use with both genetic toxicity data and for cancer bioassay data.[126]

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[123] White, P.A., et al., Quantitative Interpretation of Genetic Toxicity Dose-Response Data for Risk Assessment and Regulatory Decision-Making: Current Status and Emerging Priorities, Environmental and Molecular Mutagenesis 61:66-83 (2020).
[124] ICH Q3C (R5) (2011); ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (March 2017).
[125] White, P.A., et al., Quantitative Interpretation of Genetic Toxicity Dose-Response Data for Risk Assessment and Regulatory Decision-Making: Current Status and Emerging Priorities, Environmental and Molecular Mutagenesis 61:66-83 (2020).
[126] Id.

2. The Benchmark Dose Method provides a suitable PoD (Point of Departure), i.e. mutagenicity, for making quantitative risk assessments of mutagenic impurities.

With respect to quantitative dose-response analyses for the determination of mutagenic potency, several authors have highlighted advantages of the BMD approach to provide a PoD.[127] The point of departure (PoD) approach is a useful technique for defining acceptable exposure limits in humans.[128] The PoD is the point on a dose-response curve established from experimental data from which extrapolation below which the PoD may be employed, in conjunction with the application of uncertainty factors, for low-dose risk assessment and determination of an acceptable exposure level. For example, it is essential that a PoD should have a measure of precision or uncertainty,[129] and the BMD has CIs; however, the NOEL does not. Furthermore, the NOEL is heavily dependent on experimental conditions, and the BMD is to a much lesser extent.[130] Johnson et al. (2014) conservatively used the lowest in vivo mutagenicity benchmark dose (BMD lower bound (BMDL)) to determine a regulatory exposure limit for the potent alkylating agents *N*-methyl-*N*-nitrosourea

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[127] Johnson, GE, et al., Derivation of Point of Departure (PoD) Estimates in Genetic Toxicology Studies and Their Potential Applications in Risk Assessment, Environmental and Molecular Mutagenesis (2014); Wills JW, Johnson GE, Doak SH, Soeteman-Hernandez LG, Slob W, White PA, Empirical analysis of BMD metrics in genetic toxicology part I: in vitro analyses to provide robust potency rankings and support MOA determinations, Mutagenesis 31(3):255-263 (2016a); Wills JW, Long AS, Johnson GE, Bemis JC, Dertinger SD, Slob W, White PA, Empirical analysis of BMD metrics in genetic toxicology part II: in vivo potency comparisons to promote reductions in the use of experimental animals for genetic toxicity assessment, Mutagenesis 31(3):265-275 (2016b); Hardy A, Benford D, Halldorsson T, Jeger MJ, Knutsen KH, More S, Mortensen A, Naegeli H, Noteborn H, Ockleford C., Update: use of the benchmark dose approach in risk assessment. EFSA Journal 15(1) (2017); White, P.A., et al., Quantitative Interpretation of Genetic Toxicity Dose-Response Data for Risk Assessment and Regulatory Decision-Making: Current Status and Emerging Priorities, Environmental and Molecular Mutagenesis 61:66-83 (2020).

[128] MacGregor et al. 2015a; MacGregor et al. 2015b.

[129] Slob 2014a; Slob 2014b.

[130] MacGregor et al. 2015a; MacGregor et al. 2015b.

(MNU) and *N*-ethyl-*N*-nitrosourea (ENU),[131] and since that time, this approach has been used

in case studies and regulatory submissions and with other genotoxic compounds.[132]

3. The Benchmark Dose (BMD) approach is a compound-specific risk analysis applicable to low-dose exposures of mutagenic impurities like NDMA and NDEA to determine a PDE.

The BMD is a dose level, estimated from the fitted dose-response curve, associated

with a specified change in response, the benchmark response (BMR). The "BMDL" is the

BMD's lower confidence bound, and this value is normally used as the PoD. The key

concepts in the BMD approach are illustrated in **Figure 9** and its legend.
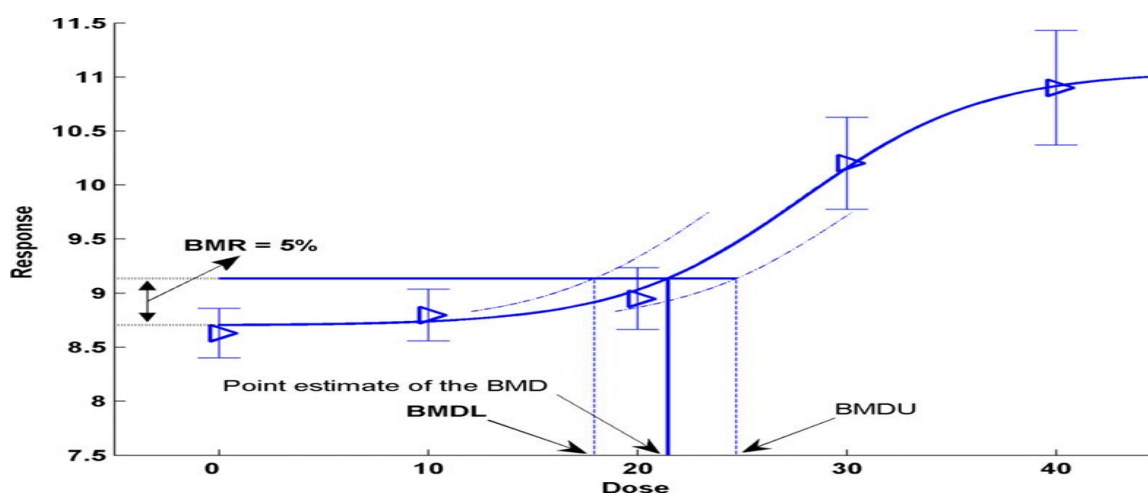

Figure 9: Benchmark dose, showing the benchmark response (BMR), BMD lower CI (BMDL), and BMD upper CI (BMDU).[133]

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[131] Johnson, GE, et al., Derivation of Point of Departure (PoD) Estimates in Genetic Toxicology Studies and Their Potential Applications in Risk Assessment, Environmental and Molecular Mutagenesis (2014).

[132] Gollapudi BB, Su S, Li AA, Johnson GE, Reiss R, Albertini RJ, Genotoxicity as a toxicologically relevant endpoint to inform risk assessment: A case study with ethylene oxide, Environ Mol Mutagen 61(9):852-871 (2020); Luijten, M., et al. (2020). "Utility of a next generation framework for assessment of genomic damage: A case study using the industrial chemical benzene." Environmental and Molecular Mutagenesis 61(1): 94-113; Kirkland DJ, Sheil ML, Streicker MA, Johnson GE, A weight of evidence assessment of the genotoxicity of 2,6-xylidine based on existing and new data, with relevance to safety of lidocaine exposure, Regul Toxicol Pharmacol 119:104838 (2021).

[133] Hardy A, Benford D, Halldorsson T, Jeger MJ, Knutsen KH, More S, Mortensen A, Naegeli H, Noteborn H, Ockleford C., Update: use of the benchmark dose approach in risk assessment. EFSA Journal 15(1) (2017).

This figure shows that a BMDL that is calculated, e.g. for a BMR of 5%, can be interpreted as follows: BMDL05 = dose where the change in response is likely to be smaller than 5%, where the term 'likely' is defined by the statistical confidence level, usually 95% confidence. The essential steps involved in identifying the BMDL for a particular study are: Specification of a response level, e.g. a 5% or 10% increase or decrease in response compared with the background response. This is called the BMR. Fitting a set of dose–response models, and calculation of the BMD confidence interval for each of the models that describe the data according to statistical criteria, resulting in a set of BMD confidence intervals. Deriving a single BMD confidence interval from the set of BMD confidence intervals for that particular adverse effect/endpoint is preferably by model averaging. An overall study BMDL, i.e. the critical BMDL of the study, is selected from the obtained set of BMD confidence intervals for the different potentially critical endpoints. In principle, the BMD approach could be applied to every endpoint measured in the relevant studies. The critical effect would then be selected in an analogous way as in the no observed effect level (NOEL) approach—that is, not only as the endpoint resulting in the lowest BMDL, but also taking additional toxicological arguments into account, just as in the case of the NOEL approach. However, it is recommended to make use of one of the strengths of the BMD approach, and select the study BMDL based on considering the complete BMD confidence intervals for the endpoints considered and combine the information on uncertainties in the underlying data with biological considerations. In the NOEL approach, the decision to accept a data set for deriving a NOEL as a potential PoD is important since poor or limited data (e.g. due to high variability within the dose groups, high limit of quantification of analytical methods, small sample sizes) will tend to result in high NOELs.

Acceptability of the data will therefore depend upon expert judgement. In contrast, the BMD approach itself provides a formal quantitative evaluation of data quality, by taking into

account all aspects of the specific data. When the data are relatively poor or uninformative, the resulting BMD confidence interval (BMD CI) for that data set will tend to be wide, and the BMDL might be much lower than the true BMD. But the meaning of the BMDL value remains as it was defined: it reflects a dose level where the associated effect size is unlikely to be larger than the BMR used. Nonetheless, it might happen that the data are so poor that using the associated BMDL as a potential PoD appears unwarranted. This might be decided when the BMD CI is wide or when different models result in widely different BMDL values.

The most well-known BMD software are the benchmark dose software (BMDS) developed by the US EPA,[134] and the PROAST software developed by RIVM[135]. When the same models are fitted to the same data using the same assumptions, BMDS and PROAST will lead to the same answer (possibly with minor numerical differences). However, there are differences in running the software (e.g. different default settings, differences in output format) and in modelling options.

4. Interpretation and properties of the NOEL and the BMD

In the BMD approach, the potential size of the effect (i.e., the benchmark response (BMR) and critical effect size (CES)) is by definition known. For human (epidemiological) data, lower BMR values may be used because the observed response is often lower than 10%. The BMD approach involves a statistical method, which uses the information in the complete data set instead of making pairwise comparisons using subsets of the data. In addition, the BMD approach can interpolate between applied doses, while the NOEL approach is restricted to these doses. Therefore, a BMDL is always associated with a predefined effect size for which the corresponding dose has been calculated, while a NOEL represents a predefined dose and the corresponding potential effect size is mostly not calculated. Therefore, a BMDL

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[134] EPA, Benchmark Dose Tools, www.epa.gov/bmds (last visited Aug. 1, 2021).
[135] PROAST, www.rivm.nl/proast (last visited Aug. 1, 2021).

value gives more information than a NOEL, by explicitly indicating the upper bound of effect

at that dose as defined by the BMR. An inherent consequence of the BMD approach is the

evaluation of the uncertainty in the (true) BMD, which is reflected by the BMD confidence

interval. This is a difference with the NOEL approach where the uncertainty associated with

the NOEL cannot be evaluated from a single data set. Furthermore, estimation approaches

such as BMD CI , provide better description of results than P-value and the statements about

significance levels[136] which includes pairwise testing and NOELs.

5. Permitted Daily Exposure (PDE) can be determined using the BMD method.

In order to use the PDE approach, "the existence of <u>mechanisms</u> leading to a dose

response that is <u>non-linear</u> or has a <u>practical threshold</u> is increasingly recognized, not only for

compounds that interact with non-DNA targets but also for DNA-reactive compounds, whose

effects may be modulated by, for example, rapid detoxification before coming into contact

with DNA, or by <u>effective repair</u> of induced damage."[137] The regulatory approach to such

compounds can be based on the identification of a NOEL and use of uncertainty factors[138] to

calculate a permitted daily exposure (PDE) when data are available (see **Figure 10**).

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[136] Lovell, Null hypothesis significance testing and effect sizes: can we 'effect' everything … or … anything?, Current Opinion in Pharmacology, Volume 51, Pages 68-77 (2020).
[137] ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (March 2017).
[138] *See* ICH Q3C (R5) (2011).

$$PDE = \frac{BMDL \times weight}{F1 \times F2 \times F3 \times F4 \times F5}$$

in most relevant animal study

typically 50kg

species extrapolation (2 – 12)

interindividual variability (10)

exposure duration (1 - 10)

severity of effect (1 - 10)

10 in case NOEL not established

Figure 10[139]: Permitted daily exposure (PDE) calculating, with NOEL/LOEL substitute for the BMDL, as a preferred PoD metric.

6. Quantitative risk assessments for mutagenic impurities are recognized by pharmaceutical regulators.

Formal deployment of quantitative methods for interpretation of mutagenicity dose-response data was pioneered by F. Hoffmann-La Roche AG following an incident that resulted in the inadvertent patient exposure to the mutagenic alkylating agent ethylmethanesulfonate (EMS).[140] In the absence of carcinogenicity data, detailed analyses of transgenic rodent ("TGR") mutagenicity dose-response data (using MutaMouse) were used to determine NOEL and threshold dose (Td) values and mode-of-action mechanisms to support a threshold-based risk assessment. Their studies were used to define (1) safety factors differentiating the NOEL and the maximum human exposure level in patients who had received EMS-contaminated nelfinavir (Viracept; later shown to be a 454-fold safety

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[139] ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (March 2017).

[140] Gocke E, Ballantyne M, Whitwell J, Müller L. MNT and MutaMouse studies to define the in vivo dose response relations of the genotoxicity of EMS and ENU. Toxicol Lett. 2009 Nov 12;190(3):286-97. doi: 10.1016/j.toxlet.2009.03.021. Epub 2009 Apr 1. PMID: 19446969; Gocke E, Müller L. In vivo studies in the mouse to define a threshold for the genotoxicity of EMS and ENU. Mutation Research. 2009 Aug;678(2):101-107. DOI: 10.1016/j.mrgentox.2009.04.005; Müller L, Gocke E. Considerations regarding a permitted daily exposure calculation for ethyl methanesulfonate. Toxicol Lett. 2009 Nov 12;190(3):330-2. doi: 10.1016/j.toxlet.2009.03.015. Epub 2009 Mar 27. PMID: 19857798; Müller L, Gocke E, Lavé T, Pfister T. 2009. Ethyl methanesulfonate toxicity in Viracept-- A comprehensive human risk assessment based on threshold data for genotoxicity. Toxicol Lett 190(3):317-329.

margin)[141] and (2) a regulatory exposure limit below which the likelihood of a mutagenic

effect was considered to have no increased risk (i.e., the PDE)[142]. Application of the

quantitative paradigm for regulatory interpretation of the MutaMouse dose-response data was

supported by evidence for a true or practical threshold response based on error-free DNA

repair by MGMT of the pro-mutagenic O^6-ethyl-guanine adducts.[143] More recently, an

analogous use of the PDE has been proposed to determine exposure limit values for

pharmaceutical impurities, including DNA-reactive mutagens.[144]

Such applications are in accordance with the following statement in the ICH M7

guideline: "The regulatory approach to such compounds can be based on the identification of

a No-Observed Effect Level (NOEL) and use of uncertainty factors (see ICH Q3C(R5),) to

calculate a permitted daily exposure (PDE) when data are available."[145]

Due to the fact that DNA repair is intrinsically linked to the mutagenic mechanism

underlying both the gene mutation and cancer dose response it is appropriate to carry out a

risk assessment that includes this information. Furthermore, the BMD and PDE also consider

the metabolism of NDMA and NDEA, and when based on the liver dose response data, the

target tissue and relevant route of exposure are also considered. This is not the case in many

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[141] Müller L, Gocke E. Considerations regarding a permitted daily exposure calculation for ethyl methanesulfonate. Toxicol Lett. 2009 Nov 12;190(3):330-2. doi: 10.1016/j.toxlet.2009.03.015. Epub 2009 Mar 27. PMID: 19857798; Müller L, Gocke E, Lavé T, Pfister T. 2009. Ethyl methanesulfonate toxicity in Viracept--A comprehensive human risk assessment based on threshold data for genotoxicity. Toxicol Lett 190(3):317-329.

[142] Müller L, Gocke E. Considerations regarding a permitted daily exposure calculation for ethyl methanesulfonate. Toxicol Lett. 2009 Nov 12;190(3):330-2. doi: 10.1016/j.toxlet.2009.03.015. Epub 2009 Mar 27. PMID: 19857798.

[143] *Id.*; Müller L, Gocke E, Lavé T, Pfister T. 2009. Ethyl methanesulfonate toxicity in Viracept--A comprehensive human risk assessment based on threshold data for genotoxicity. Toxicol Lett 190(3):317-329.

[144] Bercu JP, Galloway SM, Parris P, Teasdale A, Masuda-Herrera M, Dobo K, Heard P, Kenyon M, Nicolette J, Vock E, Ku W, Harvey J, White A, Glowienke S, Martin EA, Custer L, Jolly RA, Thybaud V, Potential impurities in drug substances: Compound-specific toxicology limits for 20 synthetic reagents and by-products, and a class-specific toxicology limit for alkyl bromides, Regul Toxicol Pharmacol 94:172-182 (2018).

[145] ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (March 2017).

of the Plaintiffs' reports, where the main focus is on a hazard-based assessment where dose

and exposure are not considered.

XII.   At the Trace Levels of NDMA and NDEA in Valsartan, There Is No Evidence That NDMA/NDEA Causes Cancer in Humans.

I have performed a risk assessment on the low levels of NDMA and NDEA impurities

found in valsartan using the BMD approach described above. Risk assessment can be carried

out on a compound-by-compound basis. For genotoxic impurities with evidence for a

practical threshold, "[t]he existence of mechanisms leading to a dose response that is non-

linear or has a practical threshold is increasingly recognized, not only for compounds that

interact with non-DNA targets but also for DNA-reactive compounds, whose effects may be

modulated by, for example, rapid detoxification before coming into contact with DNA, or by

effective repair of induced damage. The regulatory approach to such compounds can be

based on the identification of a No-Observed Effect Level (NOEL) and use of uncertainty

factors . . . to calculate a permitted daily exposure (PDE) when data are available."[146]

A.   The carcinogenicity potency data for NDMA and NDEA provides sufficient data to calculate a compound-specific Permitted Daily Exposure (PDE).

The liver has shown to be the most sensitive tissue for induction of gene mutations in

rats and mice.[147] Therefore, the rat study cancer and mutation data were selected for BMD

analysis and PDE calculations enabling comparison of PDEs for cancer and mutation in the

same species.[148] We have analysed NDMA and NDEA dose response data to determine

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[146] ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (March 2017).

[147] Jiao J, Douglas GR, Gingerich JD, Soper LM, Analysis of tissue-specific lacZ mutations induced by N-nitrosodibenzylamine in transgenic mice, Carcinogenesis 18(11):2239-2245 (1997); Gollapudi BB, Jackson KM, Stott WT, Hepatic lacI and cII mutation in transgenic (lambdaLIZ) rats treated with dimethylnitrosamine, Mutat Res 419(1-3):131-135 (1998); Akagi J, Toyoda T, Cho YM, Mizuta Y, Nohmi T, Nishikawa A, Ogawa K., Validation study of the combined repeated-dose toxicity and genotoxicity assay using gpt delta rats, Cancer Sci 106(5):529-541 (2015).

[148] Gollapudi BB, Jackson KM, Stott WT, Hepatic lacI and cII mutation in transgenic (lambdaLIZ) rats treated with dimethylnitrosamine, Mutat Res 419(1-3):131-135 (1998); Akagi J, Toyoda T, Cho YM, Mizuta Y, Nohmi T, Nishikawa A, Ogawa K., Validation study of the combined repeated-dose toxicity and genotoxicity assay using gpt delta rats, Cancer Sci 106(5):529-541 (2015).

BMDs for each nitrosamine based on existing data and applied various adjustment factors to

calculate safe human exposure limits and PDEs. The analysis also provides an opportunity to

compare PDE exposure limits derived from in vivo mutagenicity data with those from

cancer-studies for both compounds and thereby build on the experience with the use of

mutagenicity data for BMD based risk assessments. The values are subsequently evaluated

via comparisons with the default TTC for non-nitrosamines as well as for known or estimated

human exposures to nitrosamines via foods or therapeutic products (e.g., valsartan).

Using the BMD approach, the PDE were calculated for NDMA and NDEA using

gene mutation data and cancer bioassay data. Mutation data were used as proof of concept, to

show that there was potential to protect the human population based on exposure limits

derived from in vivo gene mutation data. This was successful, and PDE for both NDMA and

NDEA were calculated using the 2-year cancer bioassay data in the liver, from male and

female rats, following oral exposure, and with an extensive dose range both in the high

response and low response regions of cancer incidence.[149] BMD analysis was used to

calculate the BMD confidence intervals (BMD CI), and a conservative population size

averaging 50kg was used. However, PDE using a larger population size average of 100kg

was calculated in **Table 4** and **Figure 13** below, for comparison purposes. Composite

uncertainty factors were used, following guidance of ICH 2017[150]: F1, species extrapolation,

a default factor of 5 was used; F2, interindividual variability, a maximum value of 10 was

used to reflect DNA repair proficiency and metabolism, as a major factor; F3, exposure

duration, a factor of 1 was used for the long-term study duration (over 1 year of continuous

exposure); F4, severity of effect, since cancer is considered an irreversible effect, a maximum

value of 10 was used; F5 was set to 1, as there was no issue with database insufficiency or

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[149] Peto et al. 1991a; Peto et al. 1991b.
[150] ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals
to Limit Potential Carcinogenic Risk (March 2017).

ability to define a suitable BMDL value, which is considered superior metric than NOEL for

use in calculating the PDE.

	PDEcancer	PDEcancer	PDEcancer	PDEcancer
	NDMA	NDMA	NDEA	NDEA
BMDL10 (mg/kg)	0.062	0.062	0.022	0.022
BMDU10 (mg/kg)	0.107	0.214	0.046	0.092
Human Weight (kg)	50	100	50	100
Composite UF	500	500	500	500
PDE (mg/person/day)	0.0062	0.0124	0.0022	0.0044
PDE(µg/person/day)	6.2	12.4	2.2	4.4
PDE upper limit (µg/person/day)	10.7	21.4	4.6	9.2

Table 4: BMDL10 metrics calculated from liver cancer in Peto et al. (1991)[151] and presented in Johnson et al. (2021).[152] PDEs calculated in line with human weight and uncertainty factor (UF) best practice of ICH, with further justification presented in the recent HESI GTTC publication.[153]

Figure 11: PDE confidence intervals (PDE CI), calculated from BMDL10 and BMDU10 for each scenario. PDE were calculated from NDMA and NDEA data in Table 4, and an average population weight of 50kg or 100kg was used.

These PDE for NDMA and NDEA were calculated from the most robust cancer bioassay

study. It abided to the OECD guideline, and extended the study to allow for a very precise

dose response analysis. There was an oral route of exposure, which has high relevance when

calculating the human exposure limits for orally ingested tablets. If the drug and impurity

were taken using a nebulizer, an inhaled exposure route may be suitable, or if the drug was

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[151] Peto et al. 1991a; Peto et al. 1991b.
[152] Johnson, GE et al., Permitted daily exposure limits for noteworthy N-nitrosamines, Environmental and Molecular Mutagenesis 62:293-305 (2021).
[153] *Id.*

injected, then IP or IV could be relevant; however, those exposure routes are out of scope of the current risk assessment, where the data are excellent and relevant. The range of PDE was calculated and presented in **Figure 11**. This can be used for comparisons to human exposures of NDMA and NDEA. If the NDMA/NDEA exposure dose is within or below the PDE confidence interval, there is no evidence of an increased risk of cancer in humans. I have seen no evidence of cancer being caused in humans at the NDMA/NDEA exposure levels below the PDE. Upon review of the NDMA and NDEA levels published by FDA (Table 1), and applying the calculated PDE range described above and considering the average patient population that would be taking valsartan, it is my opinion that the level of NDMA/NDEA that a patient would reasonably be expected to be exposed to would carry no increased risk of cancer. The level of NDMA/NDEA would be proportionately reduced for the 80mg and 160mg doses of the finished product.

Notably, when the route of administration is oral exposure, the tissues downstream of the liver for metabolically activated substances like these receive much lower levels of the parent compounds and the metabolites, which reduces the amount of DNA damage and tumourigenesis in these downstream organs. Secondary mechanisms, including formaldehyde or reactive oxygen species from NDMA and NDEA, happen at negligible levels and the main risk assessment is therefore around the most potent mechanisms of the CYP-2E1 enzyme, the O^6-alkyl-G DNA adduct, the GC>AT mutation with potential for DNA repair by MGMT, multiple mutations in cancer genes and then cancer. The liver is the most sensitive tissue, and the one on which all current risk assessments are based. Where NDMA/NDEA reaches any organ downstream of the liver, if the level of NDMA/NDEA is less than the established PDE, there would be no increased risk of the mutation forming such that it could not be corrected by the DNA repair. I have seen no evidence of cancer being caused in humans where NDMA/NDEA reaches downstream organs at exposure levels below the PDE.

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Additionally, NDMA, NDEA and other alkylating N-nitrosamines have been shown to induce similar DNA adduct and mutation spectrum. When DNA is exposed to substances with similar mechanisms of action, the response is through addition. This is a standard risk assessment concept, that was also supported during the FDA 2021 expert workshop in March 2021.[154] Deviation from addition to a synergistic effect, as Plaintiffs' expert propose, is not supported. Therefore, if there were a case to assess two substances such as NDMA and NDEA together, the exposure levels for both substances would be added together, and this would be compared to the AI or PDE of the most potent out of the two substances. This is called dose addition. Any suggestion of a synergistic effect is incorrect.

B. The "Ten Key Characteristics of Carcinogens" is a hazard analysis and has no application to a risk analysis of a substance with a cancer bioassay.

The main emphasis of Dr. Panigrahy's analysis is based on 10 key characteristics of carcinogens, which have been developed as a systematic method for evaluating mechanistic data to support conclusions regarding <u>human hazard</u> to carcinogens.[155] The analysis offered by Dr. Panigrahy is a comprehensive analysis of mechanistic data, and can be used to support that NDMA is a carcinogenic hazard – but that was already known and it does not establish or even connect NDMA or NDEA to a cancer risk in humans.

Smith et al. (2016) state that "these developments will aid in advancement of future evaluations of newly introduced agents, ***including those for which mechanistic data provide the primary evidence of carcinogenicity***."[156] For NDMA and NDEA, this is not the case. The Peto et al. 1991 study is arguably the most comprehensive cancer bioassay study to be carried

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[154] FDA workshop: Nitrosamines as Impurities in Drugs; Health Risk Assessment and Mitigation Public Workshop (March 29-30, 2021), https://www.fda.gov/drugs/news-events-human-drugs/nitrosamines-impurities-drugs-health-risk-assessment-and-mitigation-public-workshop-03292021.

[155] Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al., Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis, Environ Health Perspect124(6):713–721 (2016).

[156] *Id.* (emphasis added).

out on any chemical, and therefore the Smith et al. (2016) hazard based mechanistic approach is obsolete for the risk assessment. In order to characterize the carcinogenic risk, further analyses are carried out. The main point is that this approach is used for hazard and not risk assessment. Hazard assessments are used to identify and evaluate hazards, while risk assessments are used to evaluate the consequences of exposure to something that has been identified as a hazard. In the context of NDMA/NDEA, hazard data already exists and we are now at the stage of evaluating consequences of exposure via a risk assessment, which considers dose response analysis, extrapolation of animal studies to humans, and exposure. Mechanisms underlying the main carcinogenic mechanisms can influence the risk assessment, and inform on the data used for the dose response analysis and adjustment factors used thereafter.

XIII.   The Clinical Safety of Low-Level Exposure to NDMA/NDEA Has Been Established.

The announcement in June 2018 that the EMA was "reviewing medicines containing valsartan drug substance supplied by Zhejianjg Huahai following the detection of an impurity"[157] came as a significant surprise to many, particularly as the impurity of concern was found to be an N-nitrosamine, i.e. NDMA (N-nitrosodimethylamine), and this impurity had formed as "a result of a change in the manufacturing process" during the period between 2011-2013[158]. However, as is now better understood, this low-level impurity does not present a risk to the population. Epidemiology studies since the impurities were discovered have not found any significant evidence of an increased risk of cancer(s) from this low-level exposure.

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[157] EMA, Update on review of recalled valsartan medicines: preliminary assessment of possible risk to patients, EMA/526031/2018 (2018b).

[158] Shanley A, Sartan Recalls Beg the Question: Is Compendial Impurity Testing Enough?, Pharm. Tech. 30:38-42 (2018); Christensen J, Common heart drug recalled in 22 countries for possible cancer link, cnn.com, https://www.cnn.com/2018/07/06/health/valsartan-heart-drug-recall-intl/index.html?form=MY01SV&OCID=MY01SV (last visited Aug. 2, 2021); Perscheid M, How Did N-Nitroso-Dimethylamine (NDMA) Get into Valsartan?, linkedin.com, https://www.linkedin.com/pulse/how-did-n-nitroso-dimethylamine-ndma-mm048709-get-moritz-perscheid (2020).

A recent Danish epidemiological study reported on the outcome of a clinical study assessing the increased cancer risk from patients taking valsartan products that potentially contained NDMA.[159] The final study cohort included over 5000 people, who were followed for an average of 4.6 years. The authors presumed any valsartan process changes leading to NDMA impurities were introduced during the period of 2012/2013. They further assumed that all subsequent medicinal products supplied after the process change would likely contain NDMA, i.e. a worst case scenario. The study found 104 cancer outcomes in the placebo group and 198 in the active group. The adjusted hazard ratio for overall cancer findings was 1.09 with no indication of a dose-response relationship between the various active groups (P=0.70). For individual cancer outcomes, increased cancer risk was seen for colorectal and uterine cancers. The authors recommended that longer-term studies were needed to fully assess any long-term increased cancer risk. A British Medical Journal (BMJ) editorial also called for longer-term assessment of affected patients.[160] However, CHMP did not support these proposals.[161] Firstly, they contended that "theoretical risk of cancer was very low and was itself based on a worst-case scenario."[162] Secondly, cancer screening methodologies carry additional risks for patients. Thirdly, there was still "considerable uncertainty as to which organs or tissues could be at risk from cancer."[163]

The findings of Pottegard have been replicated in another population study in Germany (Gomm, 2021[164]), where there was no increase in cancer risk, following exposure to NDMA as an impurity in valsartan and ranitidine.

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[159]   Pottegard A, et al., Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study (2018).
[160] Banzi R, Bertele V, Regulatory response to contaminated valsartan (2018).
[161] EMA, Lessons learnt from presence of N-nitrosamine impurities in sartan medicines, EMA/526934/2019 (2020a).
[162] *Id.*
[163] ICH Q3D (R1) (2019).
[164] Gomm, W, et al., N-Nitrosodimethylamine-Contaminated Valsartan and the Risk of Cancer – A Longitudinal Cohort Study Based on German Health Insurance Data, Dtsch Arztebl Int. 28;118 (2021).

XIV. Summary of Opinions

My opinions can be summarized as follows. As noted in the introduction, all of the opinions that I have offered in this report are given to a reasonable degree of scientific certainty, are based on grounds in scientifically valid reasoning and methodology, and are based on my education, training, and experience and my review of the scientific literature and materials provided in this case.

1.   I have reviewed the reports and opinions of Plaintiffs' experts as well as the materials cited in their reports. As described above, I disagree with the conclusions and opinions concerning the toxicology of NDMA and NDEA, and in particular the opinions concerning the calculation of a human exposure limit based only on the TD50 value.

2.   I performed an analysis of the toxicology characteristics of NDMA and NDEA, including the published potency data, and it is my opinion that both substances act on the same DNA sequence in a measurable and predictable manner. Further, it is my opinion that in humans, the DNA repair mechanism justifies a departure from a linear extrapolation based on animal studies, and that based on the known carcinogenicity potency of NDMA/NDEA that a permissible daily exposure level exists below which there is no increased risk of cancer in humans and above which there is not a demonstrable increased risk of cancer in humans.

3.   Based upon their toxicological properties and my review of the scientific literature, and my own research and the research of others on this very issue, it is my opinion to a reasonable degree of scientific certainty that there is no evidence that the level of NDMA and/or NDEA found in the valsartan drugs at issue can cause cancer in humans. Therefore, it is my opinion that the valsartan drugs at issue were not rendered "unreasonably dangerous" by the presence of the impurity, as Plaintiffs allege.

4.   The FDA and ICH M7 acceptable intake levels are based on a linear hypothesis. I consider DNA repair to be a threshold mechanism for NDMA/NDEA, which justifies a different human exposure level based on the PDE.

5.   The available scientific literature and evidence do not support a causal association between exposure to low doses of NDMA and/or NDEA in valsartan and the cancers alleged by Plaintiffs.

6.   The scientific evidence and the post-market literature I have reviewed does not support that the valsartan drugs at issue during the time period in question carried an independent or increased risk of cancer.

7.   It is my opinion that no scientific professional could credibly claim to a reasonable degree of scientific certainty that Plaintiffs' cancer or their alleged increased risk of cancer was caused by their treatment with the valsartan manufactured by Defendants during the time period at issue. There is no clinical data supporting the hypothesis that a less than lifetime exposure to this level of NDMA/NDEA alone poses an independent or increased risk of cancer.

These are my opinions concerning this case, and I have a sufficient factual basis and good grounds for my conclusions. I reserve the right to update this report as needed if and when additional information becomes available to me, including but not limited to additional documents, discovery, new scientific data and the depositions of Plaintiffs' experts.

I may use any of the following exhibits as a summary or in support of all of my opinions: (1) any of the materials, or excerpts there from, identified in this report and attachments, including the materials considered list; (2) excerpts from scientific articles or learned treatises; (3) demonstrative models; (4) exhibits used by Plaintiffs' experts, or other witnesses; and (5) any exhibit used in or identified at any deposition taken in this litigation.

Dated: October 1, 2021

George Johnson, Ph.D.

JOHNSON

EXHIBIT A

Dr George Johnson,
Associate Professor,
Swansea University.

Home Address: 16 Mayals Avenue, Swansea, SA3 5DE.
Telephone Number: 0044 (0) 7714653707

Awards, Achievements and Positions of Responsibility:

- Steering member of the Health and Environmental Sciences Institute (HESI), Genetic Toxicology Technical Committee (GTTC). 2013-ongoing.
- Co-chair of the HESI GTTC quantitative workgroup. 2012-ongoing.
- Co-leader of the International Workgroup on Genetic Toxicology (IWGT) 2013 and 2022, quantitative group, methods and metrics subgroup.
- Won the prestigious UK Environmental Mutagen Society (UKEMS) young scientist award in 2012 and the European EMS (EEM[G]S) young scientist award in 2014.
- Lead inventor for patent pending on artificial intelligence-based algorithms for scoring cells from the micronucleus and Cytome assays.
- President European Environmental Mutagen and Genomics Society (EEMGS, 2019-2021). Vice-President, 2017-2019. Past-President, 2021-2023.
- Committee on Mutagenicity (COM). Expert member, 2020-ongoing.
- Invited expert to EMA 2020 nitrosamine expert consultation (EMA/80573/2020)

Education and Qualifications

PhD: 'Mechanistic Investigations of the Quantitative and Qualitative Effects of Genotoxicants'
University of Wales Swansea (UWS), UK - 2002 to 2006. Completed the Thesis 10/04/2006.

B.Sc Honours Degree in Genetics - Class: 2:1
University of Wales Swansea UK - 1999 to 2002
Final Year Research Project: 'Induction of multiple centrosomes in V79 cells, after treatment with the aneugen, Bisphenol-A' - Grade 88%
Qualitative analysis of data and poster presentation skills at first conference (EEMS, 2002).
Results published in Mutagenesis (Parry et al. 2002).
Roger Gilbert Prize for excellence in final year research project

Current Employment – Swansea University

Teaching
- Developed and delivered a one-day Genetic Toxicology workshop at European Chemicals Agency (ECHA) REACH Helsinki 2011. Invited by Dr. David Bell.
- American College of Toxicology and British Toxicological Society– Practical Application of Toxicology in Drug Development. Delivered GeneTox courses run in Edinburgh, Cambridge and online, 2016-ongoing.
- Developed and delivered workshops on quantitative approaches in genetic toxicology in risk assessment and major toxicological society meetings including SOT, GTA, IGG, HESI, EEMGS and UKEMS.

- Module co-ordinator and contributor to undergraduate modules, including genetic toxicology and human and medical genetics. 2006-ongoing.
- Postgraduate teaching, PhD, MSc, MSci, MRes, 2007-ongoing.
- Director of Employability and Entrepreneurship for Swansea University Medical School, 2014-ongoing.

Research
- Collaborated with AstraZeneca, GSK, Sanofi-Aventis, Novartis, Servier and others to evaluate the *in vitro* micronucleus test 'toxicity' measures to gain a standard OECD guideline. Special issue journal of Mutation Research 2009, volume 702 Issue 2.
- Collaborated with the Japanese Pig-a ring trial group, analysis to assess inter-lab. reproducibility in support of the OECD guideline proposal (Johnson et al., 2016).
- Developed *in silico* tools to use for human health risk assessments www.MuTAIT.org
- Invited to support the ICH-M7 guideline (Wills, Johnson *et al.,* 2017, EMM).
- Recognised expert in quantitative genetic toxicology, with extensive publications in this area.
- BMD covariate work cited heavily in recent EFSA guidance (Hardy et al., 2017).
- Numerous nitrosamine papers in press and recently published.
- Expertise in developing and utilising standard and novel in vitro genetic toxicity tests.
- EMM Editor; Genes and Environment Editor; Mutagenesis 2016 Special Issue Editor.

Consultancy
Due to expertise in quantitative assessment of genetic toxicity and cancer data, recent opportunities have been taken for paid consultancy work, and this work is supported by Swansea University to date.
- Worked with 10 different pharmaceutical companies, a global food consortium, an international chemical consortium, an agrochemical company and others.
- Reports have been prepared and submitted to regulatory bodies including the European Medicines Agency, US Food and Drug Administration, European Chemicals Agency, European Food Standards Agency, Asian Drug Regulatory body and more.

Conference Platform Presentations:
Also invitations to present at CEFIC, EURL-ECVAM, Health Canada, COM, FSA, ECHA and RIVM.
1. 2003: BEMS, Geel Belgium
2. 2004: UKEMS
3. 2005: EEMS, Kos Greece.
4. 2007: FSA; UKEMS;
5. 2008: UKEMS; EEMS, Cavtat Croatia; ECETOC, Cavtat Croatia;
6. 2009: UKEMS.
7. 2010: EEMS, Oslo;
8. 2011: UKEMS, Nottingham; JEMS, Tokyo.
9. 2012: GUM, Mainz; CERLIB, Les Houches France; UKEMS;
10. 2013: SOT, San Antonio Texas; Health Canada Science Series, Ottawa; Procter & Gamble Biomed Science Seminars, Cincinnati; ICT/IUTOX, Seoul South Korea; ICEM and IWGT Brazil (and chair); IGG, UK
11. 2014: EEMS/UKEMS, Lancaster UK; ILSI-HESI GTTC workshop, Lancaster UK (and organising committee member, speaker, session chair)

12.   2015: 'how to' workshops (GTA and ILSI-HESI GTTC (and chair). Platform talks at US-GTA
        (and chair), US

ILSI-HESI GTTC US-EMGS, UK-EMS and UK-ELRIG.

13.   2016: platform talks at UK-EMS (and chair), Webinar-ACT, CPD-ACT, UK-IGG (and chair),
        European Union

Reference Laboratory for Alternative Methods to Animal Testing (EURL-ECVAM).

14.   2017: RIVM Netherlands; US-SOT; ICEM Incheon South Korea; IVTS London.

15.   2018: Vonlanthen Impurities Berlin; Die Akademie Frensius Impurities Mainz; Informa
        Impurities Berlin.

16.   2019: EEMGS Rennes, HESI-GTTC Washington DC, GUM Basel.

17.   2020: Vonlanthen Impurities Web Conference; Informa Impurities Web Conference;
        EMGS Web conference.

18.   2021: Vonlanthen Impurities Web Conference; Informa Impurities Web Conference;
        Qeplar Impurities Web Conference; ToxForum Web conference

Relevant publications

(Parry et al. 2002; Jenkins et al. 2005; Parry et al. 2005; Barber et al. 2006; Doak et al. 2007; Doak et al. 2008; Johnson and Parry 2008; Johnson et al. 2009; Marsden et al. 2009; Jenkins et al. 2010; Johnson et al. 2010a; Johnson et al. 2010b; Jenkins et al. 2011; Zair et al. 2011; Johnson 2012; Johnson et al. 2012; Seager et al. 2012; Zaïr et al. 2012; Gollapudi et al. 2013; Hernández et al. 2013; Thomas et al. 2013; Cao et al. 2014; Johnson et al. 2014; Seager et al. 2014; Zair and Johnson 2014; Johnson et al. 2015; MacGregor et al. 2015a; MacGregor et al. 2015b; Mears et al. 2015; Soeteman-Hernandez et al. 2015; Thomas et al. 2015; Avancini et al. 2016; Brusehafer et al. 2016; Johnson et al. 2016; Klapacz et al. 2016; Shah et al. 2016; Soeteman-Hernandez et al. 2016; Thomas and Johnson 2016; Tweats et al. 2016; Verma et al. 2016; White and Johnson 2016; Wills et al. 2016a; Wills et al. 2016b; Guerard et al. 2017; Rees et al. 2017; Wills et al. 2017; Verma et al. 2018; Wilde et al. 2018; Dertinger et al. 2019a; Dertinger et al. 2019b; Kirkland et al. 2019; Pottenger et al. 2019; White et al. 2019; Gollapudi et al. 2020; Heflich et al. 2020; Luijten et al. 2020; Shah et al. 2020; Steiblen et al. 2020; Wheeldon et al. 2020; White et al. 2020; Bercu et al. 2021; Chapman et al. 2021; Elder et al. 2021; Johnson et al. 2021; Kirkland et al. 2021; Padalino et al. 2021; Wheeldon et al. 2021; Wills et al. 2021a; Wills et al. 2021b)

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JOHNSON

EXHIBIT B

In re: Valsartan, Losartan, and Irbesartan Products Liability Litigation
Case No. 19-2875

GEORGE JOHNSON, PH.D.
AMENDED LIST OF MATERIALS CONSIDERED

MATERIALS CONSIDERED	BATES NOS.
MDL PLEADINGS AND GENERAL DOCUMENTS	
2019.06.17 – Amended Complaint - Master Personal Injury Complaint	N/A
2019.06.17 – Amended Medical Monitoring	N/A
2020.03.13 – Second Amended Economic Loss Class Action Complaint	N/A
2020.12.31 – Plaintiff Cancer Disclosure Type	N/A
EXPERT REPORTS (with exhibits)	
Plaintiffs' Expert Reports (with exhibits)	
2021.07.06 – Report of Mahyar Etminan	N/A
2021.07.06 – Report of Dipak Panigrahy	N/A
2021.07.06 – Report of Stephen S. Hecht	N/A
2021.07.06 – Report of Stephen M. Lagana	N/A
2021.07.06 – Report of David Madigan	N/A
Defendants' Expert Reports (with exhibits)	
2021.08.02 – Report of Michael Bottorff, PharmD, FCCP, FNLA, CLS	N/A
2021.08.02 – Report of Janice K. Britt, Ph.D.	N/A
2021.08.02 – Report of Daniel Catenacci, M.D.	N/A
2021.08.25 – Amended Report of Daniel Catenacci, M.D.	
2021.08.02 – Report of Lewis Chodosh, M.D.	N/A
2021.08.02 – Report of John M. Flack, M.D., MPH, FAHA, FASH, MACP	N/A
2021.08.02 – Report of Jon Fryzek, Ph.D., MPH	N/A
2021.08.02 – Report of Herman J. Gibb, Ph.D. MPH	N/A
2021.08.02 – Report of Lee-Jen Wei, Ph.D.	N/A
DEPOSITION TRANSCRIPTS (with exhibits)	
Company Witness Deposition Transcripts (with exhibits)	
2021.04.14 & 2021.04.15 – Transcripts of Daniel Barreto Deposition	N/A
2021.05.13 – Transcript of Anthony Binsol Deposition	N/A
2021.04.08 – Transcript of Raphael Nudelman Deposition	N/A
2021.02.26 – Transcript of Elizabeth Gray Deposition	N/A
2021.03.18 – Transcript of Stefan Karlsson Deposition	N/A
2021.03.24 – Transcript of Narendra Vadsola Deposition	N/A
2021.04.27 – Transcript of Claire Lyons Deposition	N/A
2021.05.26 – Transcript of Pan Lin Deposition	N/A
Plaintiffs' Experts' Deposition Transcripts (with exhibits)	
2021.08.05 – Transcript of David Madigan	N/A
2021.08.13 – Transcript of Stephen Lagana	N/A
2021.08.17 – Transcript of Stephen Hecht	N/A
2021.08.24 – Transcript of Mahyar Etminan	N/A
2021.09.09 & 2021.09.10 – Transcript of Dipak Panigrahy	N/A
Defendants' Experts' Deposition Transcripts (with exhibits unless noted)	
2021.09.14 & 2021.09.15 – Transcript of Lee-Jen Wei	N/A

2021.09.13 & 2021.09.14 – Transcript of Daniel Catenacci	N/A
2021.09.16 – Transcript of Michael Bottorff	N/A
2021.09.23 – Transcript of Janice Britt (rough without exhibits)	N/A
2021.09.28 – Transcript of John Flack (rough without exhibits)	N/A
2021.09.29 & 2021.09.30 – Transcript of Herman Gibb (rough without exhibits)	N/A
2021.09.29 & 2021.09.30 – Transcript of Lewis Chodosh (rough without exhibits)	N/A
REGULATORY GUIDANCES AND DOCUMENTS	
2019.01.28 – Combined N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) Impurity Assay	N/A
2018.12.11 – Combined Direct Injection N-Nitrosodimethylamine (NDMA) and NNitrosodiethylamine (NDEA) Impurity Assay	N/A
2019.04.19 – Combined Direct Injection N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA), N-Nitrosoethylisopropylamine (NEIPA), N-Nitrosodiisopropylamine (NDIPA), and N-Nitrosodibutylamine (NDBA) Impurity Assay by GC-MS/MS	N/A
2019.04.29 – Combined Headspace N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA), N-Nitrosoethylisopropylamine (NEIPA), and N-Nitrosodiisopropylamine (NDIPA) Impurity Assay by GC-MS/MS	N/A
2019.05.21 – Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) Method for the Determination of Six Nitrosamine Impurities in ARB Drugs	N/A
2019.07.24 – Development and validation of a RapidFire-MS/MS method for screening of nitrosamine carcinogen impurities N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA), N-Nitrosoethylisopropylamine (NEIPA), N-Nitrosodiisopropylamine (NDIPA), NNitrosodibutylamine (NDBA) and N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in ARB drugs	N/A
2008.12.00 – Guidance for Industry – Genotoxic and Carcinogenic impurities in drug substances and products: Recommended approaches	N/A
2008.12.16 – Federal Register Vol 73 – No 242 Summary – FDA announcing the availability of a draft guidance for industry entitled "genotoxic and Carcinogenic Impurities in Drug Substances…."	N/A
2012.06.00 - Guidance for Industry S2(R1) Genotoxicity Testing and data interpretation for pharmaceuticals intended for human use.	N/A
2015.06.09 - M7(R1) addendum to ICH M7: assessment and control of DNA reactive impurities in pharmaceuticals to limit potential carcinogenic risk.	N/A
2017.03.31 - ICH Harmonised Guideline - assessment and control of DNA impurities in pharmaceuticals to limit potential carcinogenic risk	N/A
ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (March 2017)	TEVA-MDL2875-00118444
ICH, ICH Draft Consensus Guideline, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, M7, Step 2 Version (2013).	N/A
2018.03.02 – M7(R1) assessment and control of DNA reactive impurities in pharmaceuticals to limit potential carcinogenic risk – guidance for industry	N/A
2020.06.29 – ICH M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk – Questions and Answers	N/A

2020.10.02 – FDA Webinar – Overview of the guidance for industry: control of nitrosamine impurities in human drugs	N/A
2021.02.00 – Control of nitrosamine impurities in human drugs – guidance for industry	N/A
2021.03.29 – Nitrosamines as impurities in drugs; health risk assessment and mitigation workshop, https://www.fda.gov/drugs/news-events-human-drugs/nitrosamines-impurities-drugs-health-risk-assessment-and-mitigation-public-workshop-03292021	N/A
2018 FDA, FDA Posts Laboratory Test Results of NDMA Levels, 10/2/18	N/A
2000 FDA, N-Nitrosodimethylamine - Hazard Summary	N/A
2019 FDA, Laboratory analysis of valsartan products	N/A
2015 FDA, M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to limit Potential Carcinogenic Risk Guidance for Guidance" – May, 2015 – 2015WL 4652900 (F.D.A)	N/A
2019 FDA, Laboratory analysis of valsartan products	N/A
2008 FDA, Guidance for Industry Process Validation: General Principles and Practices" 2008	N/A
FDA, News Release: FDA Updates recalled valsartan-containing product information (Aug. 9, 2018).	N/A
Rijksinstituut voor Volksgezondheid en Milieu Ministerie van Volksgezondheid, Welzijn en Spor, PROAST, https://www.rivm.nl/proast	N/A
2017 EPA 2017 Technical Fact Sheet of N-Nitroso-Dimethylamine (NDMA)	N/A
2014 EPA, Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation	N/A
2014 N/A, (EPA) Technical Fact Sheet N-Nitrosodimethylamine NDMA	N/A
2011 (EPA) Regulatory Determinations for the Third Drinking Water Contaminant Candidate List	N/A
EPA, Benchmark Dose Tools, www.epa.gov/bmds	N/A
2018 EMA (European Medicines Agency), Valsartan: Review of Impurities Extended to Other Sartan Medicines	N/A
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